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A review of the effects of tobacco smoking on the treatment of prostate cancer

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Literature Review

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Abstract

Background: Prostate cancer is the most commonly diagnosed malignancy and the third leading cause of death among Canadian men. The standard treatment modalities for prostate cancer include prostatectomy, radiation therapy, hormonal therapy and chemotherapy or any combination depending on the stage of the tumour. However, several studies have reported that tobacco smoking at the time of diagnosis and during treatment can potentially impact treatment efficacy, outcome and patients quality of life after treatment.

Materials and methods: This narrative literature review elucidates the impacts of tobacco smoking on prostate cancer progression, treatment efficacy, including its effects on prostatectomy, radiation therapy and chemotherapy, risk of cancer recurrence and mortality and quality of life after treatment. Furthermore, we discuss the importance of integrating a smoking cessation programme into the treatment regimen for prostate cancer patients in order to yield more favourable treatment outcomes, reduce risk of recurrence and mortality and increase the quality of life after treatment for prostate cancer patients.

Conclusions: Smoking cessation is one of the most important interventions to prevent cancer and it is also essential after the diagnosis of prostate cancer to improve clinical outcomes. All prostate cancer patients should be advised to quit tobacco use since it can potentially improve treatment response rates and survival, as well as reduce the risk of developing treatment complications and potentially improve the quality of life after treatment. There are several benefits to smoking cessation and it should become an important component of the cancer care continuum in all oncology programmes, starting from prevention of cancer through diagnosis, treatment, survivorship and palliative care. Evidence-based smoking cessation intervention should be sustainably integrated into any comprehensive cancer programme, and the information should be targeted to the specific benefits of cessation in cancer patients.

Introduction

Prostate cancer is the most commonly diagnosed malignancy and the third leading cause of death among Canadian men. In 2020, it is estimated that 23,300 new cases will be diagnosed and 4,200 prostate cancer deaths will occur in Canada.[1,2] The standard treatment modalities for prostate cancer include surgery (prostatectomy), radiation therapy, hormonal therapy and chemotherapy or any combination depending on the stage of the tumour.[3,4] However, several studies[5–50] have reported that tobacco smoking at the time of cancer diagnosis and during treatment will negatively impact treatment efficacy and outcome. Kassim et al.,[28] Prueitt et al.[39] and Enokida et al.[8] have reported on the adverse health effects of tobacco smoking and the impact of tobacco-related carcinogens on various cancers, including its effects on treatment outcomes, treatment efficacy, risk of metastasis, risk of recurrence and patients' quality of life after treatment. According to Prueitt et al.,[39] the nicotine in tobacco smoke is associated with increased interleukin 8 expression which may increase the risk of cancer metastasis. They reported that the nicotine in tobacco smoke has been shown to hasten metastasis in mice models with transgenic adenocarcinoma of the mouse prostate (which is closely associated with the pathogenesis of the human prostate) and can potentially accelerate the spread of human prostate cancer cells.[39] When compared to non-smokers and former smokers, Prueitt et al.[39] reported that current smokers present an elevated level of tumour-infiltrating B cells which could enhance cancer progression. Enokida et al.[8] reported that the molecular effect of tobacco smoking that potentially affects prostate cancer outcome is the 5′-Cystonie-phosphate-Guanine-3' hypermethylation as tobacco smoking is correlated with multigene hypermethylation which could influence the progression of prostate cancer. Other investigators[39,51] have also suggested that the many thousands of chemicals, including a plethora of carcinogens, in tobacco smoke can potentially cause inflammation of the prostate which partly explain the impacts that tobacco

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smoking has on prostate cancer. De Nunzio et al.[52] recently reported that tobacco smoking can also potentially promote adverse prostate cancer outcomes through multiple mechanisms, including inflammation, exposure to carcinogens, hormonal changes, increased tumour angiogenesis and genetic mutations. Prezioso et al.[53] showed some evidence that testosterone and estradiol are involved in prostatic cell promotion and tumour growth mechanism, and Fowles and Dybing 2003[54] reported that the multiple carcinogenic compounds present in tobacco such as aldehydes, benzene, metals (cadmium, arsenic, beryllium and lead), nitrosamines and polycyclic aromatic hydrocarbons (PAHs) are capable of producing cell proliferation, genotoxicity and inflammation.

Although the direct association between tobacco smoking and prostate cancer incidence and progression is not yet fully determined, however, tobacco smoking is known to cause high-grade cancers and can increase the risk of prostate cancer-specific mortality. Several studies[5–50] have demonstrated that tobacco smoking at cancer diagnosis and during treatment can negatively impact treatment efficacy, increase the risk of mortality, decrease quality of life after treatment and increase risk of recurrence. Therefore, the aim of this narrative literature review is to elucidate the impacts of tobacco smoking on prostate cancer progression, treatment efficacy, including its effects on prostatectomy, radiation therapy and chemotherapy, risk of cancer recurrence and mortality and patient quality of life after treatment. Furthermore, we discuss the importance of integrating a smoking cessation programme into the treatment regimen for prostate cancer patients in order to ensure more favourable treatment outcomes, reduce risk of recurrence and mortality and increase the quality of life for prostate cancer patients.

Tobacco Smoking and Treatment of Prostate Cancer

Several studies[5–7,9–18,20–38,40–50] have investigated the impact of tobacco smoking on the various treatment modalities including radiation therapy, surgery and chemotherapy for prostate cancer and have reported that tobacco smoking at cancer diagnosis and during treatment can potentially affect patient survival, treatment efficacy, disease recurrence and quality of life. Huncharek et al.[21] reported that tobacco smoking is associated with worse prognosis and higher prostate cancer-specific mortality regardless of the treatment method. Kenfield et al.[29] conducted a study to assess the relationship between tobacco smoking and smoking cessation with overall survival, prostate cancer-specific mortality and biochemical recurrence among men with prostate cancer and demonstrated that tobacco smoking at the time of prostate cancer diagnosis is associated with higher rate of disease recurrence and increased disease-specific and overall mortality regardless of the treatment approach. Similarly, Moreira et al.[55] have indicated that tobacco smoking is associated with more advanced disease at the time of radical prostatectomy, and Joshu et al.[27] reported higher biochemical disease recurrence after radical prostatectomy among smokers. According to a review by Ganesh et al.,[11] there is strong evidence of higher overall mortality, biochemical recurrence and enhanced adverse effects following surgery, radiation therapy and hormone therapy in current smokers diagnosed with prostate cancer.

Effect of Tobacco Smoking on Radiotherapy of Prostate Cancer

Radiation therapy is a common and effective treatment modality to treat the intact prostate or prostate bed (post-prostatectomy) for low- and intermediate-risk patients with localised prostate cancer or to include the affected lymph nodes for high-risk patients with potential lymph nodes involvement.[4,56–63] It is also an effective salvage therapy for biochemical recurrence following prostatectomy. Tobacco smoking while receiving radiation therapy is reported to be associated with poor treatment outcomes in prostate cancer patients.[5,9,11,25,29,37,44] Steinberger et al.[44] evaluated the impact of tobacco smoking on the overall treatment course of prostate cancer, assessed whether tobacco smoking increases toxicity from external beam radiotherapy in patients with regional prostate cancer and also evaluated the impact of smoking status (current smokers versus former smokers) on treatment-related toxicities or tumour-control outcomes in 2,156 prostate cancer patients with smoking histories. They concluded that, after definitive external beam radiotherapy, current smokers were at greater risk of disease metastasis, biochemical recurrence and increased mortality, and both former and current smokers were at increased risk of toxicity to the genital and urinary organs. Foerster et al.[9] conducted a systematic review and meta-analysis that consisted of 11 studies with 22,549 patients with prostate cancer undergoing primary radical prostatectomy or radiotherapy to investigate tobacco smoking and its effect on disease metastasis, biochemical recurrence and mortality. They reported that patients with localised prostate cancer who were smokers during the course of radiotherapy were at increased risk of metastasis, biochemical recurrence and increased mortality. In another study, Pantarotto et al.[37] assessed the impact of tobacco smoking on 434 prostate cancer patients receiving radical external beam radiotherapy and reported that former and current smokers had a higher risk of cancer metastasis. Tobacco smoking during radiation therapy has also been associated with a greater risk of developing long-term complications and increased side effects.[5] Alsadius et al.[5] administered questionnaires to 985 prostate cancer survivors who were treated with radiotherapy between 1993 and 2006 and collected information about their smoking status and any long-term side effects they may have developed after treatment. They reported that in comparison to non-smokers, current smokers who were treated with external beam radiotherapy were more likely to report abdominal cramps, 'defecation urgency', faecal incontinence, diarrhoea and incomplete emptying of the bowel.

Effect of Tobacco Smoking on Surgical Treatment of Prostate Cancer

Radical prostatectomy remains the gold standard and an effective treatment option for early stage prostate cancer and it is usually the first line of therapy for localised prostate cancer. Modern technological advancements in surgical techniques and the significant reduction in surgical complications and perioperative morbidity associated with radical prostatectomy have resulted in this procedure, being the most common treatment option selected by men with localised prostate cancer.[18,24,33,40] However, tobacco smoking has been shown to negatively impact the outcomes of these surgical procedures, including increased postoperative healing complications, reduced tissue repair, reduced quality of life (e.g., dyspnoea, fatigue and pain), increased length of hospital stay, increased mortality, delayed wound healing, tissue flap necrosis, wound and sutured tissue dehiscence, and surgical site infections.[13,17,27,41,43,45–47,64] Tobacco smoking has also been reported to have adverse effects on the immunological systems, wound healing and longer-term complications such as fistulas, lack of bone fusion and incisional hernia; however, cessation of

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smoking before surgery has been shown to help improve postoperative outcomes.[16,17,34,45] Tandara and Mustoe[45] reported that many clinical observations strongly supported by experimental evidence in animals have led to the conclusion that wound healing is delayed under tissue hypoxia which may result from acute exposure to tobacco smoke, and Greif et al.[15] demonstrated that smoking is a significant risk factor for surgical-wound infection. According to Schmidt-Hansen et al.,[42] the presence of carbon monoxide and cyanide in the bloodstream as a result of tobacco smoking reduces oxygen transport and inhibits mitochondrial oxidative metabolism, which are the major contributing factors to tissue ischaemia, wound breakdown and infection. Smoking also decreases collagen synthesis and interferes with the intercellular transfer required for the synthesis of proper connective tissue, and consequently adversely affecting the wound healing process.[26,48] According to Hawn et al.,[17] the acute exposure to tobacco smoke and the accumulated chronic toxic effects of tobacco smoking may adversely affect pulmonary function, which could lead to postoperative respiratory failure or pneumonia.

Sorensen[43] conducted a systematic review to investigate the effect of smoking and smoking cessation on wound healing and the impact and reversibility of smoking on the mechanisms involved in the healing processes following surgery and reported that smokers have more postoperative healing complications compared to non-smokers. He found that necrosis was four times more frequent in smokers than non-smokers, and surgical site infection, dehiscence, healing delay, hernia and lack of fistula and bone healing occurred two times more frequently in smokers than in non-smokers. Furthermore, he reported that tobacco smoking has significant impact on all phases of wound healing and the microenvironment of tissues, and it enhances thrombus formation, alters the function of inflammatory cells leading to connective tissue degradation due to excessive protease release and reduced protease inhibition, reduces the ability to control bacterial wound contamination and postoperative surgical site infection and reduces epidermal regeneration and neovascularisation. Moreover, tobacco smoking also reduces collagen synthesis and deposition of mature collagen; induces impairment of proliferation and remodelling which explains the delayed healing, dehiscence of sutured tissue and wounds, and incisional hernia; causes detrimental vasoactive effect on peripheral tissue blood flow, oxygenation and aerobe metabolism; and causes oxidative stress which has multiple biological effects, including interference with the molecular and cellular mechanisms of wound healing.[43] In a systematic review and meta-analysis conducted by Foerster et al.[9] on the association of tobacco smoking status with biochemical recurrence, metastasis and cancer-specific mortality among patients with localised prostate cancer undergoing primary radical prostatectomy, current and former smokers had a significantly higher risk of biochemical recurrence, metastasis and cancer-specific mortality. Hawn et al.[17] assessed the attributable risk and potential benefit of smoking cessation on surgical outcomes in 393,794 patients stratified by current, prior and never smokers. They reported that compared to both never and prior smokers, current smokers had significantly more postoperative pneumonia, surgical site infection and deaths. They observed a dose-dependent increase in pulmonary complications based on pack-year exposure with greater than 20 pack-years leading to a significant increase in smoking-related surgical complications. They concluded that current smokers had more adverse perioperative events, particularly respiratory complications, and that smoking cessation interventions could potentially reduce the occurrence and costs of adverse perioperative events.

Effect of Tobacco Smoking on Chemotherapy of Prostate Cancer

Nicotine in tobacco smoke is reported to induce resistance to chemotherapy-induced apoptosis in various cell lines by modulating mitochondrial signalling, and the inhibition of this signalling can potentially impact treatment efficacy since many cancer therapies induce apoptosis through the mitochondrial pathway.[7,36] This suggests that nicotine has the potential to reduce the efficacy of chemotherapeutic agents by stimulating these survival pathways. Therefore, patients who continue to smoke throughout chemotherapy treatment have an increased risk of inhibiting the mitochondrial pathway, which is important in the metabolism of chemotherapeutic drugs, thus increasing the potential for limited response and disease progression.[7,36] Moreover, tobacco smoke is also known to alter the rates of metabolism for several chemotherapeutic drugs, especially those involving the cytochrome P450 (CYP) and glucuronide conjugation pathways; therefore, if patients continue to smoke while on chemotherapy, higher concentrations of the drugs will be required in order to be effective.[32] According to Kroon,[32] many drugs are substrates for hepatic CYP1A2 and their metabolism can be induced in patients who smoke and can lead to clinically significant decrease in pharmacologic effects; thus, patients who smoke may require higher doses of drugs that are CYP1A2 substrates. O'Malley et al.[36] have reported that tobacco smoke-associated PAHs can induce key drug-metabolising enzymes of cytochrome P450 and isoforms of the glucuronyl transferases families and have been demonstrated in both in vitro and animal models. In addition, the tar in tobacco is also known to contain several carcinogens including N-nitrosamines, aromatic amines and over 500 PAHs and these PAHs are oxidised by cytochrome P450 enzymes and the resultant metabolites can exert mutagenic effects on the DNA.[6,10,20,23,35] According to O'Malley et al.,[36] the induction of the metabolising enzymes could lead to accelerated clearance with resultant impact on systemic therapy efficacy and toxicity in smokers compared with non-smokers. Kroon[32] also reported that tobacco smoke contains PAHs which are known to induce key drug-metabolising enzymes of cytochrome P450 (CYP) and the induction of these enzymes may lead to accelerated clearance with resultant impact on systemic therapy efficacy and toxicity in patients who smoke. Moreover, several chemotherapeutic drugs and newer targeted therapies are also metabolised by the uridine 5′-diphosphate-glucuronyl transferases leading to accelerated clearance and reduced systemic effect.[36] According to O'Malley et al.,[36] although the exact mechanism behind the accelerated drug metabolism is still not clear, there is emerging evidence that compounds in tobacco smoke may epigenetically modify these enzymes that result in persistently elevated activity. Moreover, there may be a direct effect of nicotine on the molecular effectors of cellular apoptosis induced by several chemotherapies drugs.[36]

Several studies[7,28,32,36,38,49] have demonstrated that tobacco smoking or exposure to tobacco smoke can potentially interfere with the pharmacokinetics and metabolism of anticancer drugs such as docetaxel, erlotinib, imatinib, paclitaxel, toremifene and vinblastine and can also affect the incidence and severity of adverse events and efficacy of chemotherapy. Zevin and Benowitz[49] have reported that tobacco smoking can affect drug therapy by both pharmacokinetic and pharmacodynamics mechanisms. According to Petros et al.[38] although the potential effects of tobacco smoke on the processes that determine the pharmacokinetic disposition of drugs are complex, tobacco smoke contains

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chemicals such as cadmium and arsenic that can induce endogenous metallothioneins, which could potentially alter the pharmacokinetic disposition of some anticancer drugs. Furthermore, they found that the mechanisms of these interactions are likely related to smoking induced acceleration of the activity of cytochrome P450 (CYP) enzymes, induction of drug glucuronidation by uridine 5′-diphosphate–glucuronosyltransferases (UGT) and increased concentrations of circulating drug-binding protein. Zevin and Benowitz[49] also reported that the PAHs in tobacco smoke are responsible for the induction of cytochrome P450 (CYP) 1A1, CYP1A2 and possibly CYP2E1, and these enzymes induced by tobacco smoking may increase the risk of cancer by enhancing the metabolic activation of carcinogens. Dresler[7] reviewed studies investigating the effects or potential effects of tobacco smoking on cancer treatment outcomes and reported that carbon monoxide in tobacco inhibits CYP enzymes in vitro and demonstrated a dose–response effect. Furthermore, they indicated that smokers generally have carbon monoxide levels in excess of 8–10 ppm and nicotine levels between 4 and72 ng/ml and potential chemicals such as hydrogen cyanide, methane, acetaldehyde, methyl chloride, acetic and formic acids, or benzene which are not clinically monitored but have the potential to negatively impact the efficacy of chemotherapy. Kroon[32] reviewed the mechanisms for drug interactions and clinically significant pharmacokinetic and pharmacodynamics drug interactions with smoking and reported that numerous drug interactions exist with smoking; therefore, smokers taking a medication that interacts with smoking may require higher doses than non-smokers; however, upon smoking cessation, smokers may require a reduction in the dosage of an interacting medication.

Effect of Tobacco Smoking on Hormone Levels in Men with Prostate Cancer

Prostate cancer is considered a hormone-dependent cancer, and Pierorazio et al.[65] and Kosti et al.[66] have reported on the modifications on sexual hormonal bioavailability caused by tobacco smoking. Some studies[12,14,30,31,41,67] have reported that tobacco smoking may affect certain hormone levels in men and such endocrine disturbances may eventually change the prostate-specific antigen (PSA) levels, and high PSA levels suggest that smoking promotes the progression of prostate cancer. Koc et al.[30] investigated the effects of tobacco smoking on the PSA in men aged 25–35 and 50–70 years and reported that both young and older men who smoke had higher levels of PSA compared to non-smokers. Gray et al.[14] investigated the associations between PSA and PSA derivative levels and smoking status and found that tobacco smoking was associated with decreased levels of free PSA (fPSA) and free/total PSA ratio (%fPSA) and that tobacco smoking is a risk factor for prostate cancer. Kristal et al.[31] examined whether tobacco smoking is associated with PSA levels and the rate of PSA increase (PSA velocity) in men over 55 and reported significantly lower PSA levels and substantial differences in PSA velocity in smokers compared to non-smokers. Other studies[12,67,68] have also reported that tobacco smoking can potentially influence prostate carcinogenesis through its effect on levels of other hormones, for example, high levels of testosterone and low levels of oestrogens and sex hormone binding globulin have been shown to increase risk of prostate cancer. Furthermore, other hormones such as cortisol, androstenedione, plasma testosterone, dihydrotestosterone and sex hormone binding globulin are reported to be significantly higher in smokers than non-smokers. According to Prezioso et al.,[53] there is some evidence that hormones such as testosterone and estradiol are involved in prostatic cell promotion and tumour growth mechanism.

Tobacco Smoking and Risk of Prostate Cancer Recurrence

Numerous studies[11,27,29,55,69–71] have investigated the impact of tobacco smoking on disease recurrence and have reported strong evidence of higher overall biochemical recurrence in current smokers diagnosed with prostate cancer; however, some studies also noted that smoking cessation over a 10-year period may ultimately lead to better treatment outcomes. Darcey and Boyle[69] conducted a systematic review and meta-analysis to investigate the associations between tobacco smoking and prostate cancer-specific recurrence and concluded that tobacco smoking at prostate cancer diagnosis is associated with a significantly increased risk of recurrence. Joshu et al.[27] investigated the relationship between smoking and prostate cancer recurrence in a cohort of 1,400 men treated with radical prostatectomy. They reported that survivors who were smokers 1 year after receiving surgery were more likely to experience prostate cancer recurrence than never and former smokers. Kenfield et al.[29] also analysed the relationship between tobacco smoking and biochemical recurrence and observed a greater risk of prostate cancer recurrence in current smokers after adjusting for stage and grade of disease at presentation. Furthermore, they stated that men who had quit smoking for 10 years or more at the time of diagnosis had similar risk of recurrence to never smokers. However, men with less than 20 pack-years and less than 10 years of smoking history had similar risks to current smokers. Similarly, Rieken et al.[72] found that smoking was associated with recurrence of prostate cancer and that men who were smokers within the last 10 years were at increased risk of recurrence while men who stopped smoking more than 10 years before their radical prostatectomy had the same risk as never smokers. Moreira et al.[55] also concluded that the risk of biochemical recurrence was greater in current smokers than in former and never smokers. Ngo et al.[70] analysed the impact of tobacco smoke on recurrence in 630 men who underwent radical prostatectomy and reported that heavy smokers, those with a history of 20 pack-year or more, were at a greater risk of recurrence in comparison to light smokers, those with less than 20 pack-year history, and non-smokers, thus suggesting a dose–response relationship. Moreover, Oh et al.[71] studied 1,165 men who underwent radical prostatectomy without any neoadjuvant or adjuvant therapy between 2004 and 2010 and demonstrated that prostate cancer patients with body mass indexes greater than 25 kg/m^2 and who were current smokers experienced a decrease in biochemical recurrence-free survival.

Tobacco Smoking and Survivorship or Risk of Prostate Cancer-Specific Mortality

Most prostate cancer patients are cured of the disease through the various treatment modalities (i.e., radiotherapy or prostatectomy); however, for some men, the journey continues even after treatment, and the months and years following treatment (the survivorship period) present a new set of challenges. Cancer survival refers to the percentage of people who are still alive at some point in time after their cancer diagnosis while cancer mortality refers to the number of deaths due to the cancer.[1,2] Several studies[21,22,69] have reported an association between tobacco smoking and prostate cancer-specific mortality, suggesting that tobacco smoking could potentially play a significant role in prostate cancer progression. Darcey and Boyle[69] conducted a systematic review and

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meta-analysis to investigate the associations between tobacco smoking and prostate cancer-specific mortality and concluded that tobacco smoking at prostate cancer diagnosis is associated with a significantly increased risk of overall mortality and prostate cancer-specific mortality. Based on their analysis of the studies which investigated the impact of current versus never smokers on mortality, they observed that current smokers were at a 79% increased risk of prostate cancer-specific mortality.[69] Huncharek et al.[21] also conducted a meta-analysis of 24 cohort studies to investigate tobacco smoking and risk of mortality from prostate cancer. They reported that patients who were current smokers were at a 17% increased risk of mortality from prostate cancer compared to non-smokers and the risk increases to about 24–30% for heavy smokers. Based on meta-regression models, Islami et al.[22] demonstrated a dose–response relationship between tobacco smoking and prostate cancer-specific mortality. Moreover, Giovannucci et al.[12] analysed the relationship between smoking and fatal prostate cancer and concluded that smokers had a lower survival rate and men who quit smoking for a period of 10 years or more were no longer at a higher risk of mortality. Kenfield et al.[29] also observed similar results and suggested that men who quit more than 10 years prior to prostate cancer diagnosis had similar lower risk of mortality as men who never smoked. Gong et al.[73] investigated the association between smoking at the time of cancer diagnosis and prostate cancer-specific mortality in 752 men and reported that smokers were more than twice as likely to die from prostate cancer in comparison to never smokers, while no differences were found between never and former smokers. In addition, they observed that those who quit within 10 years of cancer diagnosis had a modest increase in risk of mortality while those who had quit for more than 10 years were at a decreased risk of mortality.[73] De Nunzio et al.[52] evaluated the available evidence of the role of tobacco smoking in prostate cancer development and progression and reported an association between the number of cigarettes smoked by current smokers and prostate cancer-specific mortality. They observed that cigarette smoking is associated with an increased risk of prostate cancer-specific death where the number of cigarettes smoked per day had a dose–response association with prostate cancer-specific mortality.

Tobacco Smoking and Quality of Life after Cancer Treatment

Tobacco smoking has been shown to be associated with poor quality of life for prostate cancer survivors.[11,40,74–79] Alsadius et al.[5] reported that current smokers treated with external beam radiotherapy and brachytherapy were at increased risk of long-standing symptoms such as diarrhoea and incontinence, whereas no differences in symptoms were observed between former and never smokers, suggesting that smoking significantly impacts patients' quality of life. Solanki et al.[79] investigated the impact of tobacco smoke on the development of late gastrointestinal and genitourinary toxicities in 633 men who were treated with external beam radiotherapy between 1988 and 2008 and concluded that current smokers had about 2·7–3 times greater risk of experiencing genitourinary toxicity after therapy. Dieperink et al.[76] investigated the impact of tobacco smoking on the quality of life of 317 prostate cancer survivors treated with conformal radiotherapy and androgen deprivation therapy using the Expanded Prostate Cancer Index Composite (EPIC-26) and the 12-Item Short Form Survey (SF-12) questionnaires and found that current smokers experienced poorer general and disease-related quality of life (specifically suffering from bowel issues). They reported significant negative associations between smoking and self-assessed late adverse effects after radiotherapy for prostate cancer. The mean urinary incontinence score was lower in smokers compared to non-smokers, and smoking was found to reduce the mean bowel score and the mean sexual score. Furthermore, on the SF-12, smoking reduced the mean Physical Component Summary score and the mean Mental Component Summary score, and current smokers had increased risk of moderate-to-severe problems with SF-12 vitality, the EPIC bowel overall problems and EPIC sexual overall problems. Ditre et al.[77] examined the association between smoking status and several pain-related outcomes among 224 cancer patients undergoing chemotherapy using self-reported measures of pain severity, pain-related distress and pain-related interference. They reported that patients who continued to smoke after cancer diagnosis experienced more severe pain than never smokers and current smokers reported greater interference from pain than either former or never smokers. Phillips et al.[78] investigated the effect of lifestyle on sleep disturbances among 288 cancer patients undergoing chemotherapy using a self-report measure system and reported significantly worse sleep disturbances among current smokers compared to never smokers. In a systematic review conducted by De Nunzio et al.[52] to assess the impact of tobacco smoking on prostate cancer development and progression, they reported an association between tobacco smoking and aggressive prostate cancer and lower quality of life in smokers receiving external beam radiotherapy. They concluded that smokers present a higher risk of biochemical or distant failure after prostate cancer treatment.

Integration of Smoking Cessation Programmes into Prostate Cancer Treatment Regimen

Several studies[5–55,64–81] have demonstrated the association between continued tobacco smoking after cancer diagnosis and increased risk of treatment complications, disease metastasis, secondary cancers, prostate cancer-specific mortality and biochemical recurrence; reduced treatment efficacy or need for increased treatment dose and decreased quality of life in men with prostate cancer. Existing evidence strongly suggests that integrating a smoking cessation programme into prostate cancer treatment regimen is key to ensuring better treatment outcomes and better overall quality of life for current smokers. Therefore, in order to enhance clinical outcomes, smoking cessation interventions programmes should be integrated throughout the prostate cancer care continuum including prevention and screening, diagnosis and treatment of localised and advanced disease, survivorship and palliative care. It is evident that any advice given in the context of medical care is an effective cessation tool and therefore every interaction with a patient and their family should be an opportunity to discuss positive lifestyle choices, including tobacco cessation. Thus, during each initial patient consultation, health professionals should screen patients for tobacco use, counsel patients and their relatives about the health benefits of quitting smoking and recommend appropriate hospital or community-based smoking cessation programmes. Patients should also be encouraged to seek individual counselling with their primary health-care professionals or other trained health experts. All health promotion strategies for smoking cessation should be focused on providing the patient with

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the most appropriate intervention that fosters positive lifestyle choices. Health professionals, including medical and radiation oncologists, nurses and radiation therapists, should all play an important role in assessing smoking cessation for patients since interventions by healthcare professionals have been shown to be effective in increasing the rate of abstinence in cancer patients.[80,81]

Conclusions

Tobacco smoking is the leading cause of cancer mortality and continues to be a major public health problem. Although the exact molecular mechanisms linking tobacco smoking and prostate carcinogenesis is still not clear, several studies strongly suggest an association of tobacco smoking and increased risk of treatment complications, disease metastasis, secondary cancers, recurrence, toxicity, poorer prognosis, potential reduction in treatment efficacy, lower response rate, increased prostate cancer-specific mortality, reduced overall survival, decreased disease-free survival, increased biochemical recurrence and decreased quality of life in men who continue to smoke. However, there is also enough evidence from numerous studies strongly suggesting that quitting tobacco smoking will ensure better treatment outcomes and better overall quality of life for current smokers. Therefore, it is imperative that prostate cancer patients are supported to quit tobacco use in order to get the potential benefits of improved treatment response rates and survival, as well as reduce the risk of developing treatment complications and potentially improve quality of life after treatment. Smoking cessation programmes should be integrated into the prostate cancer care continuum and prostate cancer patients should be screened and counselled to participate in interventions tailored specifically to their health needs in order to optimise clinical outcomes. Smoking cessation programmes have the potential to improve treatment outcomes, reduce symptom burden after treatment, reduce various risks associated with tobacco smoking, limit the likelihood of treatment interruptions and improve patients' quality of life after cancer treatment.

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Conflicts of Interest. The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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