Minireview

Cancer Prevention Research

Scented Candles as an Unrecognized Factor that Increases the Risk of Bladder Cancer; Is There Enough Evidence to Raise a Red Flag?

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Abstract

The causes of bladder cancer are not yet fully uncovered, however the research has identified a number of factors that may increase the risk of developing this cancer. The chemical carcinogenesis of bladder cancer due to chronic exposure to aromatic hydrocarbons has been well-established. The identification of this correlation led to an improvement of safety measures in chemical industry and a gradual decrease of bladder cancer cases among workers. Nevertheless, in the majority of bladder cancer cases, the specific cause of the disease still can't be specified. It makes the question of unrecognized factors associated with bladder cancer development even more relevant. Taking under consideration known chemical carcinogenesis of bladder cancer, this minireview takes under investigation the possible link between using scented candles and a risk of bladder cancer development. Burning scented candles contain many of the substances that are associated with a bladder cancer. Furthermore the scented candles are not only very popular but also widely available on the market, with limited quality regulations and unspecified raw materials determining a spectrum of potentially dangerous substances emitted during burning.

Introduction

Bladder cancer is the sixth most commonly occurring cancer in men and the 17th most commonly occurring cancer in women. According to GLOBOCAN 2018 annual report, more than half million of new bladder cancer patients were recorded globally in 2018, accounting for 3% of all new cancer cases. The 5-year survival rate is 76% in the United States, and 68% in Europe, but survival tends to be better in higher income than lower income countries (1). The exact cause of bladder cancer is unknown but proven risk factors for bladder cancer include smoking tobacco, industrial exposure to aromatic amines, diesel exhaust fumes, or chronic inflammation within the urinary bladder. Debatable risk factors comprise of dietary intake of fruit and vegetables or long-term exposure to arsenic-contaminated or chlorinated drinking water (2). Many of the recognized risk factors can be modified by proper lifestyle measures and protective initiatives, implying a strong prospect for intervention. Prevalence of hazardous chemical agents that increase the risk of bladder cancer is extensive in the everyday environment, and thus exposure to them is not confined to particular occupational groups. We should be concerned about the unrecognized sources of potentially carcinogenic chemicals that may be present in our households.

Indoor air pollution is mainly generated by combustion, building material, and bioaerosols. This is one of the leading health problems in developing countries (3). On the other hand, are households in developed countries free of indoor pollution sources, or are they not identified yet? Seemingly, safe-scented candles when burned indoors, can release a large number of volatile organic compounds acknowledged as occupational bladder carcinogens. Scented candles, widely used for relaxation purposes, may emit plenty of biologically active substances that are inhaled and gradually accumulate in urine, analogously to compounds found within tobacco smoke (4).

In this article, we discussed the hypothesis of whether scented candles burned indoors might be a relevant source

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of different hydrocarbons involved in urinary bladder carcinogenesis. An occasional use of scented candles and hence related neglectable emission is not likely to exert any carcinogenic effect. On the other hand, frequent burning of scented candles for years and using them within poorly ventilated rooms may hypothetically increase the risk of bladder cancer.

Chemical Carcinogenesis of Bladder Cancer

The relationship between exposure to chemical agents and the development of bladder cancer was established in 1895 by Rehn who reported the increased occurrence of these diseases among workers in the aniline dye industry in Germany. Subsequent research determined that aromatic hydrocarbons, in particular, nitrite derivatives, were chemical agents responsible for the carcinogenic transformation of urinary bladder epithelium (urothelium; ref. 5). The metabolism of aromatic hydrocarbons is based on esterification by acetyltransferase and/or glucuronidation by UDP-glucuronidase (6). The resulting metabolites become water-soluble substances transported by the blood and excreted in the urine. In this form, they can penetrate urothelial cells and interact with DNA to form DNA adducts exerting a genotoxic effect. The exact contribution of the respective aromatic hydrocarbon metabolites to urinary bladder carcinogenicity is not yet determined. The major DNA repair pathways such as base excision repair, nucleotide excision repair, and double-strand break are gradually compromised during this process (7). Neutralization of absorbed carcinogenic hydrocarbons occurred by a systemic guarding mechanism utilizing liver enzymes such as cytochrome p450 (CYP1A2), N-acetyltransferase 2 (NAT2), and glutathione S-transferase M1 (GSTM1; ref. 8). Although these enzymes are also present in the urothelial cells, they characterize with lower activity and do not provide enough protection in case of chronic exposure. Unfortunately, the dose–response relationship of irreversible DNA damage is linear down to background concentrations and a no-effect level is difficult to define (9).

The accumulation of various molecular changes causes the development of bladder cancer (10). Loss of heterozygosity on chromosome 9 is a crucial event in the transition of normal urothelium to papillary transitional cell carcinoma, while the loss of p53 is primarily involved in the development of carcinoma *in situ* (11). These mutations or chromosome aberrations were reliably linked to exposure of aromatic hydrocarbons when investigating carcinogenesis of hematological cancers (12).

Candle Fumes

Different substances are emitted as gases from scented candles being burned indoors. They vary significantly from those that are potentially carcinogenic, to those with no known health effect. Studies conducted in environmental test chambers proved that the emission of combustion gases such as carbon monoxide or nitrogen oxide would pollute the indoor environment (13). The more significant concern is the presence of measurable amounts of aldehydes, different polycyclic aromatic hydrocarbons including benzene or toluene, dibenzodioxins, and dibenzofurans in candle fumes that are products of wax, aroma substances, or combustion dyes (14). There reports indicating that people who were exposed to scented candles mainly complained about vertigos, headaches, mucosa irritation, respiratory problems, and dry or irritated throat. Concentrations of pollutants [formaldehyde, CO_2, CO, PM2.5, PM10, and volatile organic compounds (VOC)] measured indoor during burning of scented candles, exceeded background concentrations indicating that the candles were the source of contamination (15). According to public health authorities, regular burning of several scented candles indoors can expose us to harmful amounts of organic chemicals (16).

Commonly available scented candles, especially the cheaper varieties, are made from paraffin-based wax and may emit carbonyl and aromatic compounds. Ahn and colleagues provided a summary of substances identified in the commercially available scented candles. A total of 34 compounds, including potentially carcinogenic formaldehyde and aromatic hydrocarbons such as toluene and benzopyrene were found in high abundance (17). Formaldehyde, characterized with a low boiling point, was generated at a high concentration. In addition to low wax quality, aroma candles also contain artificial scents and dyes that release different chemicals when burned. Also, dyes containing benzidine which is associated with urothelial cancer development are still used to color candle waxes (18).

According to available data, measured benzene and naphthalene concentrations emitted by burning candles were below the standards considered to exert a toxic biological effects. Conversely, sulphur dioxide (SO_2) and benzopyrene concentrations might exceed the recommended values. Derudi and colleagues compared the concentrations of potentially carcinogenic substances emitted by different tested candles. They exposed significant discrepancies with generated pollution (19). In the case of one tested candle, worryingly, the use of it would lead to severe overexposure to SO_2 and benzopyrene. Similarly, Orecchio and colleagues found significant differences in emitted pollutants from scented candles (20). Measured benzopyrene levels in fumes derived from 12 tested candles ranged from 0.1 to 7.5 ng/m^3. The guideline value for benzopyrene concentration recommended by the World Health Organization (WHO) is 1 ng/m^3 (21). The available reports indicated that the scented candles' fumes are a heterogenic mixture of VOCs, whose composition

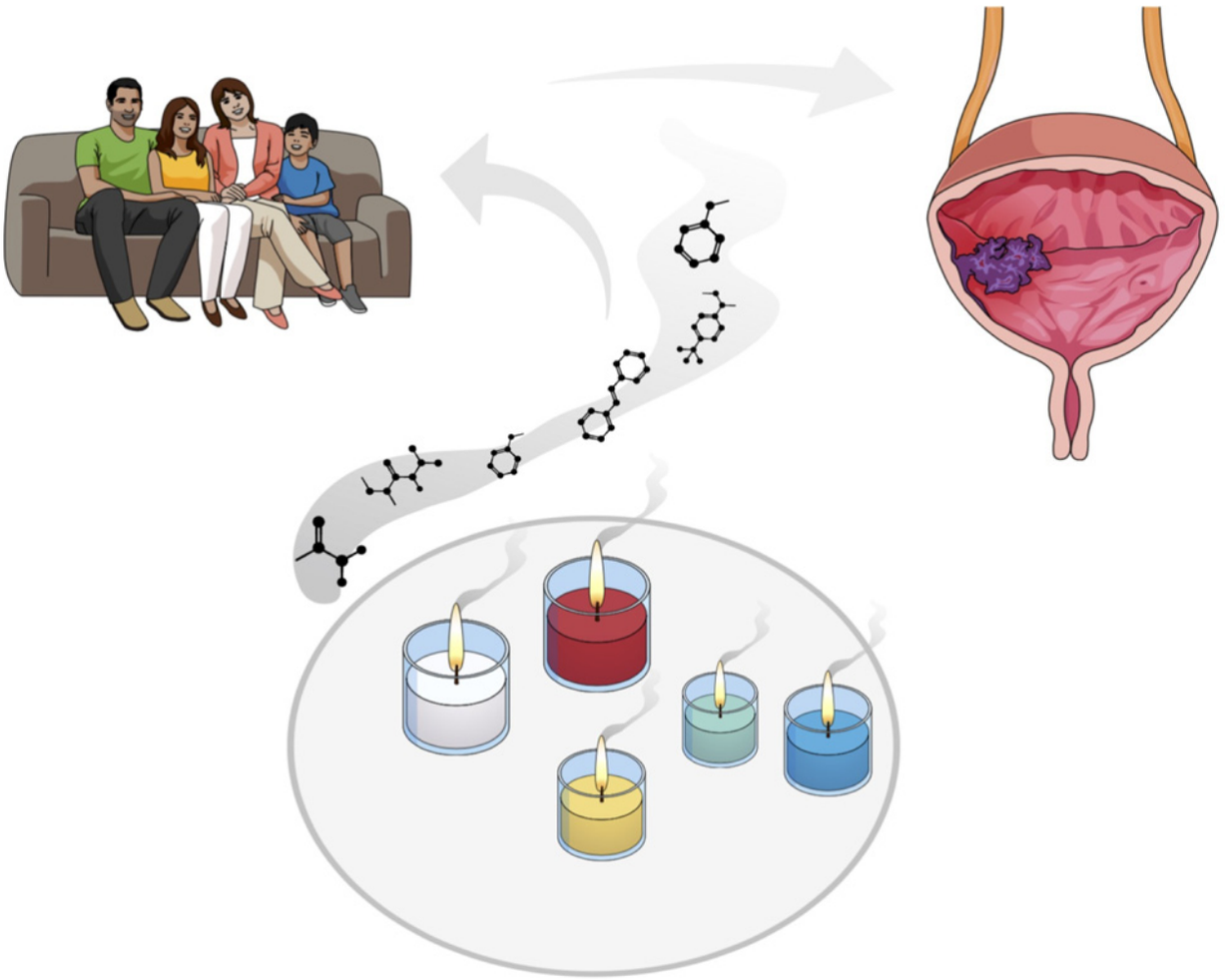

Figure 1.
Scented candles as risk factor for bladder cancer. Scented candles, widely used for relaxation purposes indoors, are source of VOC including substances associated with urothelial carcinogenesis. The long-term use of scented candles in inadequately ventilated rooms may be a risk for bladder cancer.

varies significantly due to differences in the composition of raw materials (Fig. 1).

VOCs Related to Bladder Cancer

Benzenopyrene and aromatic hydrocarbons

The United States Environmental Protection Agency (EPA) described benzopyrene as one of the most mutagenic and genotoxic aromatic hydrocarbons based on *in vivo* animal studies (22). In humans, occupational exposures to benzopyrene and aromatic hydrocarbons primarily by inhalation have been associated with bladder cancer (23). The emitted aromatic hydrocarbons concentration for scented candles was between 2.3 and 49.8 μg/kg (20).

In comparison, the aromatic hydrocarbons limit tolerated by the European Commission in dairy products is 35 μg/kg (24). Derudi and colleagues indicated that the concentration of benzopyrene emitted by burned scented candle indoor may reach about 40% of the recommended value (25). Scented candles therefore should be recognized as a potential source of hazardous pollutant, which is particularly significant in households with increased benzopyrene contamination with, for example, tobacco smoke or old-fashioned heating solutions. Gu and colleagues indicated chromosome 9p21 as a molecular target for benzopyrene-induced chromosome aberration associated with the risk of bladder cancer (26). The same mechanism is confirmed to be responsible for colorectal adenoma formation in patients with elevated benzopyrene intake (27).

Aromatic hydrocarbons are ligands for the aryl hydrocarbon receptor (AhR), which acts as a cytosolic ligand-activated transcriptional factor governing the cell cycle

and differentiation (28). Al-Dhfyan and colleagues recently explained the mechanism of linking extensive AhR activation with the promotion of carcinogenesis (29). They showed using a model of breast cancer stem cells that increased activity of AhR/CYP1A1 inhibited PTEN and simultaneously induced β-Catenin and Akt pathways. These changes controlled the development, self-renewal, and proliferation of cancer stem cells. The same constellation intracellular signaling disturbance was also reported in invasive bladder cancer (30). Knowing inductive relationship between aromatic hydrocarbons and universal carcinogenic pathways, alarming is the fact that these substances with high boiling point may be emitted by scented candles even before they lit (17).

Interestingly Borze and colleagues postulated synergistic effects of aromatic amines and polycyclic aromatic hydrocarbons on urothelial carcinogenicity (31). In this context, small but chronically inhaled scented candle fumes might increase the risk of urothelial cancer development in people already exposed to aromatic amines. It may be a potential room for improvement for public health institution to inform people who are occupationally exposed to chemicals to limit their use in households. For this purpose, the sources of hazardous substances must be established in details. Another disturbing thought is that in some world regions dietary intake of polycyclic aromatic hydrocarbons contributes to 90% of total allowed exposition level (32).

SO_2

Several pollution studies that evaluated environmental carcinogens indicated that prolonged exposure to SO_2 pollution at low concentrations might increase the risk of bladder cancer (33). Interestingly, in this study, high exposure to SO_2 in contrast to low one was not associated with bladder cancer risk (HR 0.9). Authors did not explain this observation. In our opinion, this is the best example of difficulties in interpretation due to inconsistency in epidemiologic research data aimed to assess cancer risk factors.

The exact mechanism, however, explaining SO_2 contribution to carcinogenesis in humans has not been postulated yet. It might, however, disrupt IL6 signaling and create a favorable environment for chronic inflammation-induced mutagenesis (34).

Formaldehyde

In 1987, the U.S. EPA classified formaldehyde as a probable human carcinogen under conditions of unusually high or prolonged exposure (35). Since that time, some studies concluded that formaldehyde exposure was associated with certain types of cancer, including bladder (36, 37). Even though there is not any known mechanism linking formaldehyde to bladder carcinogenesis, exposure to formaldehyde is occasionally postulated to be a risk factor for bladder cancer with an unknown risk threshold (38). Elevated formaldehyde concentrations were reported in patients who have bladder cancer (39). Recently, the safety of e-cigarettes was also questioned in terms of bladder cancer induction (40). One of the suspected substance is formaldehyde that may be emitted at high levels during e-cigarette vaping (41). Formaldehyde is an ingredient of candles' fragrances, and as a substance with low boiling point it is released at high concentration, which may considerably exceed acceptable threshold value time-weighted average. It was pointed out that formaldehyde contamination is characteristic for scented candles in comparison with decorative ones (19).

Essential oils and artificial fragrance ingredients

Scented candles are available in various fragrances obtained by mixing different odor substances. To achieve relaxing properties for aromatherapy, essential oils or artificial fragrant ingredients are applied. Essential oils are a concentrated, hydrophobic fraction obtained from aromatic plants widely used in the cosmetic industry. They contain multiple substances belonging to various chemical classes such as alkaloids, flavonoids, saponins, steroids, and terpenoids that determine biological activity (42). Among bioactive substances derived from essential oils, many may have a beneficial therapeutic effect, but on the other hand, some of them could also be hazardous to health.

Interestingly, most of the available studies are focused on evaluating their hidden medicinal properties while analyzing potential risks seems to be ignored. For instance, the three isothiocyanates (allyl, benzyl, and phenylethyl) found in papaya (*Carica papaya L*) or mustard (*Brassica nigra*) essential oils induced bladder cancer in rats (43–45). Isothiocyanates inhibit dealkylation of pentoxyresorufin and ethoxyresorufin in microsomes, which are mediated predominantly by cytochrome p450 (CYP2B1; ref. 46). It is the critical stage of the detoxification pathway in the liver and urothelial cells. CYP2B1 is one of the significant isozymes involved in the activation of the tobacco carcinogen 4-(methylnitrosamino)-1-(3-pyridyl)-1-butanone (47). In these circumstances inhaled isothiocyanates generated by scented candles may have an additive carcinogenic potential with tobacco smoke.

According to industry reports, 75% of scented candles are fragranced with artificial scents because they cost considerably less (48). According to the Environmental Working Group, 95% of chemicals used in synthetic fragrances are derived from petroleum and include benzene

derivatives, that is, toluene that belongs to primary urothelial carcinogens (49). Apart from these cardinal substances causing bladder cancer, phthalate esters were also identified in synthetic fragrances (50). Huang and colleagues suggested that exposure to phthalates might contribute to the development of urothelial cancer in patients with chronic kidney disease (51). They found that higher urinary concentration of Mono(2-ethyl-5-hydroxyhexyl) phthalate was correlated to the increased risk of carcinogenesis within the urothelium. MEHHP is a urinary metabolite of di-(2-ethylhexyl) phthalate which is a common substrate of artificial fragrances also used to produce scented candles.

Epidemiologic Point of View

The objective of candle emission studies is to identify and quantify hazardous chemicals emitted under standardized and reproducible conditions for the purpose of human health risk assessment. Applied analytical technics, however, varied in protocols especially regarding to combustion environment (19, 52). Consequently, obtained heterogenic emission profiles are difficult to compare. As far as average VOC concentrations emitted by matched candles in the studies were concerned, candles fumes did not raise safety concern (13, 19, 20, 25). But does this data lull us into a false sense of security? Among tested scented candles there was usually one in each report which emitted VOC exciding legal values in terms of at least one pollutant (benzopyrene, chrysene, etc.; refs. 19, 25). Unfortunately, in general, the candle emissions of benzene and nitric amines being the most notable risk factors for development of bladder cancer, were below levels to be recognized as carcinogenic. On the other hand, the threshold limit values are not consistent and may paradoxically hamper giving a clear recommendation, if analytic methodologies are not coherent. Following WHO recommendation, benzene toxicity threshold cannot be established, and thus guideline air values should be as low as possible (53). At the same time, the European Union has established an EU ambient air pollution limit for benzene 5 mg/m^3 (54). After screening only few available researches that focused on carcinogenic agents emitted by scented candles, it is noticeable that the ranges of emitted agents were quite wide. It implicated that measured emission profile was dependent on many variable factors impacting candle combustion and research methodology. The number of simultaneously burned candles, their size, origin or room humidity, and ventilation, influenced measured VOC indoor air concentration. Worth noticing is the fact that in most of research aimed to determine indoor air VOC levels, it was assumed that scented candles burned in a 30-m^3 room, whereas average rooms in Europe were below this size (55). Moreover, from the behavioral point of view, many of us are used to burn scented candles in small bathrooms or bedrooms.

Despite undertaken effort to reliably elucidate the carcinogenic risk of using scented candles, there is still some dose of uncertainty. Most of researches included in conclusion section statement indicate that results should be critically interpreted and further research is necessary due to current methodology limitations. To obtain useful data for formulation of future guidelines, the case–control studies should be planned to correlate candle fumes exposure with urine levels of carcinogenic compounds.

Systemic Problem

Manufacturers of scented products, including candles or plug-in air freshener are not required to disclose all ingredients in the United States and European Union. Uhde and colleagues demonstrated that even more than 90% of substances were not declared because of insufficient industry supervision (56). The Federal Drug Administration and the European Medicines Agency do not have the authority and resources to evaluate the presence of dangerous ingredients in all scented products available on the market. Gas chromatography-mass spectrometry is the only method which can determine the chemical composition (57). In many cases scented candles are released on the market based on the producer's declaration that the particular product was made in compliance with required standards that are formulated. Moreover, no law exists that would oblige manufacturers to prove the safety of their product. As a consequence chemical substances, potentially containing harmful compounds, are outside the jurisdiction of public health institutions.

Discussion

Identification of as many possible bladder cancer risk factors is crucial for public health as the incidence of newly diagnosed cases each year is gradually rising. Scented candles are a heterogenic group of products which are the source of indoor pollution. In this situation, public awareness of the potential relationship between substances emitted by scented candles and bladder cancer is an essential step for better prevention. Considering this risk, it might be wise to introduce easy to comply with preventive measures. Accordingly, the room should be ventilated after using scented candles to eliminate the accumulated chemical substances generated during burning. We should pay attention to the quality of the scented candles used and try to avoid ones of poor quality made from paraffin or artificial substances. New regulations of labeling and packaging are necessary, where manufacturers of scented candles

would be required to provide a brief statement or pictogram informing the consumer about indoor pollution risk and other related health problems. It is very important to draw the attention of consumers of these products to the importance of reading the labels, so that they can get a sense of the chemical composition of the product they are buying.

Disclosure of Potential Conflicts of Interest

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