



Commentaries

Could the endocrine disruptor bisphenol-A be implicated in the pathogenesis of oral and oropharyngeal cancer? Metabolic considerations and future directions

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ABSTRACT

Bisphenol-A (BPA), a prototype endocrine disrupting molecule, has been associated with many disease entities such as diabetes mellitus, obesity, polycystic ovarian disease, cardiovascular disease, reproductive and neurodevelopmental disorders. BPA has also been associated mainly with not only hormone sensitive cancers such as breast, prostate, endometrial, ovarian, testicular and thyroid cancers but also non-hormonal sensitive cancers such as cervical and lung cancers, osteosarcoma and meningioma. Recent research has investigated the sources of contamination which are responsible for higher BPA concentrations in the oral cavity and oropharyngeal space, representing the first site of BPA exposure after ingestion. Besides growing awareness and case registration, the incidence and prevalence of oral (OC) and oropharyngeal cancer (OPC) have increased during the last decades correlating with the increased production of BPA worldwide. So far, no study in the medical literature has explored the association of BPA with OC and OPC. BPA may be linked to the etiopathogenesis of OC and OPC through a multitude of mechanisms encompassing and interconnecting genetic, epigenetic, inflammatory, immune, metabolic, hormonal and oxidative stress alterations as well as modulation of oral microbiome. Hence, it is not possible to rule out a potential role of BPA exposure in oral and oropharyngeal tissue carcinogenesis, especially knowing its potential to participate in other non-hormonal sensitive malignancies and to deregulate signaling pathways implicated in OC and OPC. This perspective aims at outlining evidence and proposing for the first time a potential link between BPA with OC and OPC, the most frequent subtypes of head and neck malignancies.

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1. Introduction

Endocrine disrupting chemicals (EDCs), such as pharmaceuticals, dioxin and dioxin-like compounds, polychlorinated biphenyls, DDT and other pesticides, components of plastics such as bisphenol A (BPA) and phthalates,

and polycyclic aromatic hydrocarbons, are either naturally occurring or chemically synthesized substances, detected in various concentrations in the domestic environment and, as their name suggests, interfere with hormonal systems [1,2]. EDCs exert their effects on target tissues by either mimicking the effects of endogenous hormones or by blocking them,

Abbreviations: Akt, v-Akt murine thymoma viral oncogene homolog; AP-1, Activator protein 1; bax, BCL2-Associated X Protein; BC, breast cancer; bcl-2, B-cell lymphoma 2; bcl-xL, B-cell lymphoma-extra Large; BMI, body mass index; c-Raf, cellular Rapidly Accelerated Fibrosarcoma; BPA, Bisphenol A; DES, diethylstilbestrol; DMAP1, DNA Methyltransferase 1 Associated Protein 1; DNA, Deoxyribonucleic Acid; DNMT1, DNA (cytosine-5)-methyltransferase 1; EDC, Endocrine Disrupting Chemical; ELISA, Enzyme-linked Immunosorbent Assay; ER, estrogen receptor; ERK 1/2, extracellular signal-regulated kinase 1/2; EZH, Enhancer of Zeste Homolog; FXR, Farnesyl X Receptor; HDAC, Histone deacetylase; HDL-C, High-density Lipoprotein Cholesterol; HIV, Human Immunodeficiency Virus; HNSCC, Head and Neck Squamous Cell Carcinoma; HOMA-IR, Homeostatic Model Assessment for Insulin Resistance; HOTAIR, HOX Transcript Antisense Intergenic RNA; HPV, Human Papilloma Virus; hs-CRP, high sensitive C-reactive Protein; IGF-1R, Insulin-like Growth Factor-1 Receptor; IL, Interleukin; JAK, Janus kinase; JNK, Jun N-terminal kinase; LDL-C, Low-Density Lipoprotein Cholesterol; LXR, Liver X Receptor; MAPK, mitogen-activated protein kinase; miRNA, micro-RNA; mTOR, mammalian target of rapamycin; nc-RNA, non-coding RNA; NF-κB, nuclear factor-κB; OC, oral cancer; OPC, oropharyngeal cancer; OSCC, oral squamous cell carcinoma; PI3K, phosphatidylinositol 3-kinase; PPAR, Peroxisome Proliferator-Activated Receptors; ROS, Reactive oxygen species; STAT, signal transducer and activator of transcription; TAS, Total Antioxidant Status; TNF-α, tumor necrosis factor-α.

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altering the balance of the respective systems. BPA is considered a prototype EDC molecule, as its endocrine disrupting effects have been studied extensively. BPA has been utilized in medicine as a synthetic estrogen, binding estrogen receptors, since the 1930s [2]. It was largely replaced by diethyl stilbesterol (DES) that was later banned from the FDA due to its strong links with cervical and vaginal cancer [3].

BPA is a chemical product which consists of two phenol molecules (bisphenol) connected with one acetone molecule. Its estimated annual worldwide production reaches approximately 6 million tons with an increasing trend in the coming years [4]. Due to its cross-linking properties, BPA has been used in the manufacture of polycarbonate plastics as well as of epoxy resins, and has become widely known for its heat resistance and elasticity [5]. Bis-Glycidyl dimethacrylate (bis-GMA) is the most commonly used BPA derivative as a base of dental resins. Bis-GMA has methyl methacrylate groups binded to the hydroxyl groups of BPA via glycidyl spacer. Other BPA derivatives include BPA dimethacrylate (bis-DMA), BPA diglycidyl ether (BADGE) and BPA ethoxylate dimethacrylate (bis-EMA) [6]. Some BPA derivatives, such as 3,3'-dichlorobisphenol A (3,3'-diCIBPA), tetrabromobisphenol A (TBPA) and 3,3',5,5'-tetraCIBPA are more toxic than BPA itself. Fig. 1 depicts the chemical structure of BPA and its chlorinated derivatives, which result from the reaction between BPA and free chlorine.

1.1. Endocrine Disrupting Chemicals, BPA and Disease States

EDCs, particularly BPA, have been associated with many disease entities such as diabetes mellitus (DM), polycystic ovarian disease, obesity, cardiovascular disease, thyroid and reproductive disorders, neurodevelopmental disorders and cancer [7–13] mainly in cross-sectional studies and meta-analyses. Data from the NHANES study point to a strong correlation of type 2 diabetes and exposure to EDCs including BPA, after adjustment for BMI and several other factors [14,15]. Exposure to EDCs may account for at least part of the increase in the prevalence of diabetes [2,16]. Although causality cannot be demonstrated, experimental and epidemiologic evidence suggest that environmental BPA exposure may be deleterious to humans, particularly when perinatal exposure takes place [17,18].

BPA has been shown to act through several nuclear and extra-nuclear receptors including the estrogen receptors ER α , ER β , membrane receptor GPR30, the estrogen receptor-related ERR γ and possibly the PPAR γ and the IGF-1R [19–22]. Besides these receptors, various EDCs including BPA may target androgen, glucocorticoid, thyroid hormone, liver X (LXR), and farnesyl X (FXR) receptors [2]. As a result, the highly complex and

multidimensional mechanism that regulates insulin secretion, tissue insulin sensitivity and energy homeostasis involving these receptors, can be severely challenged by the effect of these xenobiotics leading to insulin resistance [2,22]. A similar pattern of disruption occurs with a variety of EDCs, including BPA, as shown by many in vivo and in vitro experiments; when applied during specific time frames, these changes alter the controlling mechanisms of metabolism by potentially inducing alterations in the epigenome predisposing to obesity, insulin resistance or insulin secretion attenuation. Indeed, BPA exposure during gestation induced a phenotype of hyperinsulinemia and impaired glucose tolerance in the adult male offspring, partially mimicking the effects of a high-fat diet [23]. Therefore, fetal and or neonatal BPA exposure may induce adverse health effects later in life through many biological mechanisms including epigenetic modifications [18].

1.2. Association of BPA with Cancer Risk

BPA is classified as a class 1B reproductive toxin by the European Chemical Classification and Labeling while BPA diglycidyl ether, a widely used component of epoxy resins, and glycidaldehyde, a metabolite of BPA, have been classified as possibly carcinogenic (suspected class group 2B) substances based on the International Agency for Research on Cancers [13,24,25].

EDCs, particularly BPA, have been associated with cancer risk, mainly hormone-sensitive cancers such as breast, prostate, endometrial, ovarian, testicular and thyroid cancers but also non-hormonal sensitive cancers such as cervical and lung cancers, osteosarcoma and meningioma [26–28]. Indeed, the panel of experts from the National Institute of Health and the United States Environmental Protection Agency has concluded that BPA may not only be associated with neoplastic malignancies in hormone sensitive tissues [28]. However, the association between BPA and cancer risk was not evidenced in the NHANES study 2003–2004 and in certain case-control studies regarding breast cancer and uterine leiomyoma. Therefore, the available epidemiological data linking BPA to human cancer risk are unclear and controversial [29–32]. Moreover, high quality epidemiological studies are still sparse and randomized controlled trials are absent.

Mechanistic and animal experiments as well as epidemiologic studies may point to an increasing support for a carcinogenic effect due to the BPA's exposure but the resulting tumorigenesis process is complex, long standing and multifactorial; rendering, therefore, the epidemiological proof of a carcinogenic effect of BPA difficult to obtain, attributed

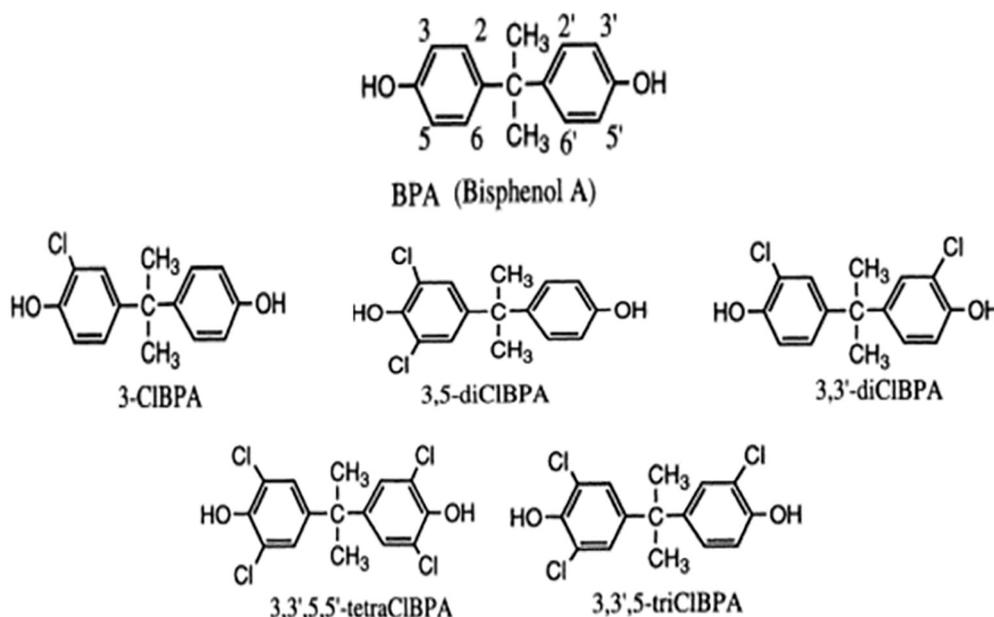


Fig. 1. Chemical structure of BPA and its chlorinated derivatives. BPA has a molar mass of 228.29 g/mol and a molecular formula C₁₅H₁₆O₂.

also to many confounding factors. Noteworthy, it is difficult to assess exposures at critical windows of early development (fetal, birth, puberty) which present the most important impact on later cancer development. This possibility cannot be excluded as BPA shows 1) limited binding capacity to plasma proteins such as α -fetoprotein, which protects tissues from excessive exposure to estradiol during development and 2) a more activated state (free BPA) and toxicity due to fetal liver immaturity [33]. Animal studies in rodents and primates have showed that early-life BPA exposure below the tolerable daily intake of 50 $\mu\text{g}/\text{kg}$ of body weight/day may increase the susceptibility to prostate and breast malignancy via oncogenic mechanisms explored, mainly, in cell lines [34,35]. It is important to note that BPA exposure displays a non-monotonic dose response curve regarding cancer, as lower and higher doses may significantly speed up breast carcinogenesis and metastasis in animal models [36].

Regarding carcinogenesis, BPA may promote transformation by estrogenic and non-estrogen dependent pathways [37]. BPA has been involved at the genetic level in multiple oncogenic signaling pathways, such as the MAPK, STAT3 and PI3K/AKT pathways, exerting proliferative and mitogenic effects [37]. More precisely, BPA is involved in the activation of pro-proliferative (such as Akt, c-Raf and ERK1/2) and anti-apoptotic genes and proteins (such as Bcl-2). BPA targets also other oncogenic mechanisms with a key role in cancer such as mitochondrial and stress response pathways [38]. Indeed, BPA is a mediator in the induction of inflammatory reactions via the MAPK family and other transcriptional factors (e.g. NF- κ B, AP-1 and STAT family), while it has an impact on immune responses by altering immune cells, e.g. mast cells, CD4+ T cells, B cells, macrophages, etc. [22]. Besides the direct genotoxic role of high-dose BPA exposure and the sensitization to DNA-damaging agents in different tissue systems, low-dose BPA exposure may indirectly be involved in tumorigenesis by affecting the genome stability via epigenetic alteration, chromosome segregation, oxidative stress and DNA damage signaling [38–41].

This perspective aims at outlining evidence and proposing for the first time a potential link between BPA exposure with oral and oropharyngeal cancer (OC and OPC respectively), the most frequent subtypes of head and neck malignancies.

2. Epidemiology of Oral and Oropharyngeal Cancer

Head and neck malignancies represent the sixth most common cancer globally, whereas OC and OPC constitute the most frequent subtypes being the eighth leading cancer in men and comprising approximately 4% of cancer cases in the United States [42,43]. Nearly 50% of patients suffering from OC and OCC present with regional or distant metastases at diagnosis with a 50% mortality rate [42,44]. As depicted in Table 1, OC incidence and prevalence are 1.4 to 3 times higher in men than women in the majority of geographical areas [44]. Although OC affects generally men in their sixth or seventh decade, there has been a significant increase in females and the younger age group under 45 years [45].

OC appears in the oral cavity, the lips or the salivary glands [42,45] while OPC involves the oropharyngeal space. Fig. 2 shows the distribution of the anatomical sites involved in OC. OC and OPC constitute two

distinctive genetical, histopathological and clinical entities comprising several histologic subtypes with oral squamous cell carcinoma (OSCC) being the predominant subtype in 90% of cases [42,44].

As depicted in Fig. 3, epidemiologic studies have shown that the main risk factors for the development of OC and OPC are tobacco smoking, alcohol consumption, viral infections, age, family history of cancer, UV radiation, low Body Mass Index (BMI) and poor nutrition especially in vegetables and fruits [46–50]. In particular, Human Papilloma Viruses (HPV) are implicated in the OSCC etiopathogenesis [46,48] with HPV-16 being related to OPC [48] and HPV-18 being associated with OC [46]. Moreover, Human Immunodeficiency Virus (HIV) is another infectious risk factor for OC, especially in Kaposi's sarcoma and non-Hodgkin lymphoma subtypes [49].

3. Sources of Contamination with BPA and Cancers in the Oral Cavity and Oropharyngeal Space

Research conducted during the last years has investigated the sources of contamination which are responsible for higher BPA concentrations in the oral cavity. BPA and its derivatives are found in dental composites, sealants [51], orthodontic adhesive resins and polycarbonate brackets [6]. Therefore, BPA can be detected in the oral cavity as a product of degradation of the aforementioned dental materials [52]. Although BPA salivary concentration is low (<10 ng/mL), it may reach higher concentrations (up to 100 ng/mL) in individuals with dental materials [53]. Moreover, since BPA is leached into the environment during production, transport as well as waste disposal and processing, inhalation, skin absorption and consumption of contaminated water can lead to an increase in its concentration in the human body, including the oral cavity. However, the most common root of human exposure to BPA is food, especially canned one [54]. BPA released from food containers, metal food cans, restaurant and packaged meals (microwave or box mixes) and plastic water bottles may contaminate food and beverages [54,55]. Factors such as heat, basic or acidic levels of pH may induce enhanced leaching of BPA from food or water containers [56]. Moreover, BPA is also found in cigarette filters, while other studies have reported associations between BPA release and use of personal care products such as mouthwash [55].

Besides growing awareness and case registration, the incidence and prevalence of OC and OPC has increased during the last decades [45] correlating with the increased production of BPA worldwide [28]. So far, no study in the medical literature has explored the association of OC and OPC with BPA, for which oral cavity and oropharyngeal space represent the first site of BPA entry after ingestion.

4. Mechanisms Connecting BPA with Oral and Oropharyngeal Cancers

BPA may promote OC and OPC through estrogenic and non-estrogen dependent pathways as displayed in Fig. 4 [37]. Although OC and OPC are not considered hormone sensitive, they may express hormonal receptors with prognostic significance [57–59]. BPA may be linked to the etiopathogenesis of OC and OPC through a multitude of mechanisms encompassing and interconnecting genetic, epigenetic, inflammatory, immune, metabolic, hormonal and oxidative stress alterations as well as modulation of oral microbiome as shown in Fig. 3. BPA may also be an additive factor of the susceptibility of cells in the oral cavity and oropharyngeal space to exposures to risk factors depicted in Fig. 3. The following mechanisms are proposed.

4.1. BPA as a Proliferative, Pro-angiogenic and Invasive Tumor Factor

As shown in Fig. 5, the development of OC is a complex procedure exhibiting tumor plasticity and heterogeneity, and leading progressively to genomic instability through genetic and epigenetic modifications [60]. Specifically, OSCC progression includes alterations in oncogenes or tumor suppressor genes. Alterations in regulatory signaling pathways,

Table 1

Epidemiologic data of oral cancer, World Health Organization Classification, 2012.

Geographical area	Incidence rate per 100,000 ASR (W) ^a		Prevalence		Mortality rate (W) ^a	
	Male	Female	Male	Female	Male	Female
Africa	3.3	2	9961	6892	2.1	1.3
Asia	5.2	2.5	111,683	56,549	3	1.4
Oceania	9.6	5.3	2279	1350	2.7	1.9
Europe	7.5	2.5	42,539	56,549	3	1.4
WHO America region	5.9	2.6	31,805	17,204	1.5	0.6
Latin America and Caribbean	4.6	2.2	12,918	7586	1.9	0.7

^a ASR (W): age-standardized incidence rate per 100,000 population structure.

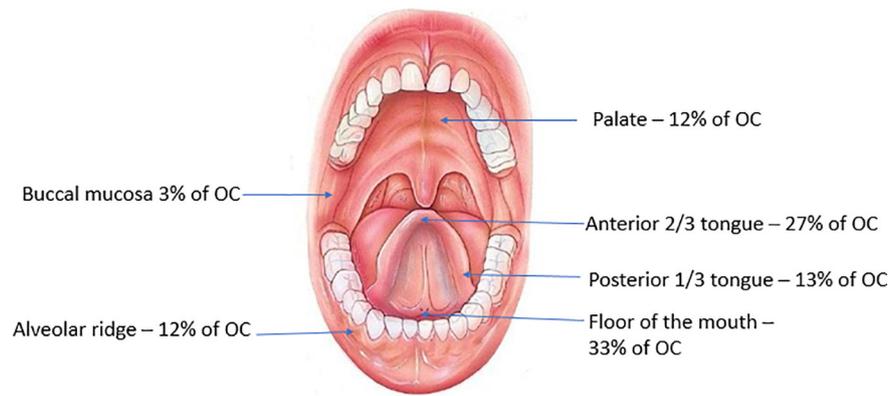


Fig. 2. Distribution of anatomical sites involved in oral cavity cancer (OC).

such as *PI3K/AKT* and *Ras/Raf/MAPK* pathways, and inactivation of *p53*, induce cell cycle dysregulation and resistance to apoptosis which in conjunction with the inhibition of growth suppressors facilitate the initiation and development of OSCC [60]. The *MAPK* signaling pathway, which includes the extracellular signal-regulated kinase (ERK)1/2, the c-Jun N-terminal kinase (JNK), the p38 and the ERK5 sub-pathways, is crucial in OC because it is associated with tumor proliferation, differentiation, angiogenesis, invasion and metastasis [61]. Furthermore, it has been found that the mutation of the *PIK3CA* gene is frequently related to head and neck cancer, while the activation of *PIK3* and of the mTOR pathways contribute to autophagy. In turn, basal level of autophagy is involved in cancer cell metastasis by preventing anoikis, which constitutes an apoptotic process linked to the detachment of cells from the extracellular matrix. Autophagy diminishes macrophage infiltration by hindering cancer cell necrosis while it prevents macrometastasis through maintaining the dormant phenotype of cancer [62]. Additionally, interactions between malignant cells and the microenvironment contribute to the progression and invasion of OSCC [60].

BPA, which binds and stimulates nuclear and membrane receptors, contributes to the regulation of cancer cell growth and proliferation as well as migration and invasion, through the *ERK1/2* and/or *Akt* signaling pathways [22]. BPA-induced migration and invasion of cancer cells has been evidenced in ovarian, lung, cervical, breast and endometrial cancer cells. Following BPA exposure, the enhanced stimulation of proteases, the loss of epithelial cell junctional proteins and the increase in mesenchymal markers like N-cadherin, fibronectin and vimentin, may induce migration and invasion of tumor cells [22]. BPA reduces apoptosis by enhancing pro-survival signals through the *PI3K/Akt/mTOR* pathway, up-regulating anti-apoptotic signals such as Bcl-2 and Bcl-xL, and decreasing pro-apoptotic molecules, such as Bax and p53 and Bim. BPA is also linked to anti-cancer drug resistance through the activation of pro-survival signaling pathways, like the *PI3K/Akt/mTOR* [22,63].

Recently, it has been shown that the incidence of endoderm-derived cancers, including OPC, is increased. Nuclear receptors' pathways, which are targeted by BPA, participate in the development of endoderm-derived glands and in carcinogenesis [38]. BPA is involved in endoderm-gland carcinogenesis and could potentially play a role in the progression of OPC, as well as in the deregulation of signaling pathways implicated in OPC.

4.2. BPA as an Epigenetic Regulator Priming for Carcinogenesis

The epigenetic mechanisms which encompass DNA methylation, histone modifications, nucleosome positioning and modifications of non-coding RNAs (ncRNAs), are crucial in maintaining the development and tissue-specific homeostasis of the organism. Deregulation of these processes results in pathologic conditions including cancer. Indeed, tumor samples of OC present increased genome-wide hypomethylation and hypermethylation of promoter areas in comparison to normal samples [64]. Several genes which present abnormal levels of expression in clinical

specimens and OC cell lines are considered to be epigenetically regulated and directly associated with OC [65]. Despite the fact that DNA hypermethylation/hypomethylation is closely connected to histone modification in OC, the later mechanism has not been thoroughly studied yet. A current study which examined the global histone modifications in patients with OSCC has revealed significant epigenetic alterations related with tumor characteristics, stage and invasion. More precisely, histone H3K4ac has been found downregulated, while histone H3K27me3 levels have been upregulated in OSCC samples [66]. Histone deacetylases (HDACs) are enzymes responsible for post-transcriptional modifications. HDAC6 was increased in most of the OSCC malignant samples and associated with cancer stage [67]. MiRNAs modifications are also vital in carcinogenesis, progression, invasion and metastasis. The miR-34 family exerts tumor suppressor properties, and similarly to miR-137, miR-193a and miR-203, has been found downregulated in OSCC cell lines. Additionally, ectopic expression of miR-137 or miR-193a in mechanistic studies of OC has enhanced cell growth due to their tumor suppressor role [64].

BPA exposure may induce epigenetic changes similar to those detected in OC samples. BPA may lead to histone modifications, hypermethylation/hypomethylation of CpG islands and expression of ncRNAs [38]. Although BPA may modify the epigenetic programming, the precise biochemical mechanisms are not well understood yet. BPA may alter the expression of DNA methyltransferases and Methyl-CpG-binding protein 2, which play a crucial role in gene expression regulation. In particular, exposure to BPA may dysregulate the expression of histone methyltransferase EZH2, which is closely related to gene silencing and chromatin condensation [68]. EZH2, which is found overexpressed in multiple types of cancers, participates in gene silencing and cancer development, while its methyltransferase activity is essential to methylate lysine-27 of histone H3 [69]. BPA may cause DNA damage with the formation of adducts. Therefore, DNA reparative mechanisms may trigger epigenetic alterations, including 1) phosphorylation of histone H2AX which is responsible for the recruitment of reparative factors, 2) de novo methylation assisted by the induction of DNA methyltransferases DNMT1 and DNMT3 and 3) increase of histone acetylation leading to a relaxation of domains in chromatin [69]. Finally, BPA may provoke alterations in long noncoding RNAs and microRNAs that participate in many biological pathways including gene silencing and gene regulation. In response to BPA exposure, increased HOTAIR (HOX Antisense Intergenic RNA) and miR-146A expression were associated with invasion and metastasis in BC cell lines [68] and compromised reparative mechanisms in transformed placental cell lines respectively [70].

4.3. BPA as a Pro-oxidant Factor

Reactive oxygen species (ROS) as well as other free radicals participate in the pathogenesis of several disease states including cancer, playing a role in the initiation, promotion and progression of cancer [71]. In tobacco chewers and smokers, the burst of ROS is associated

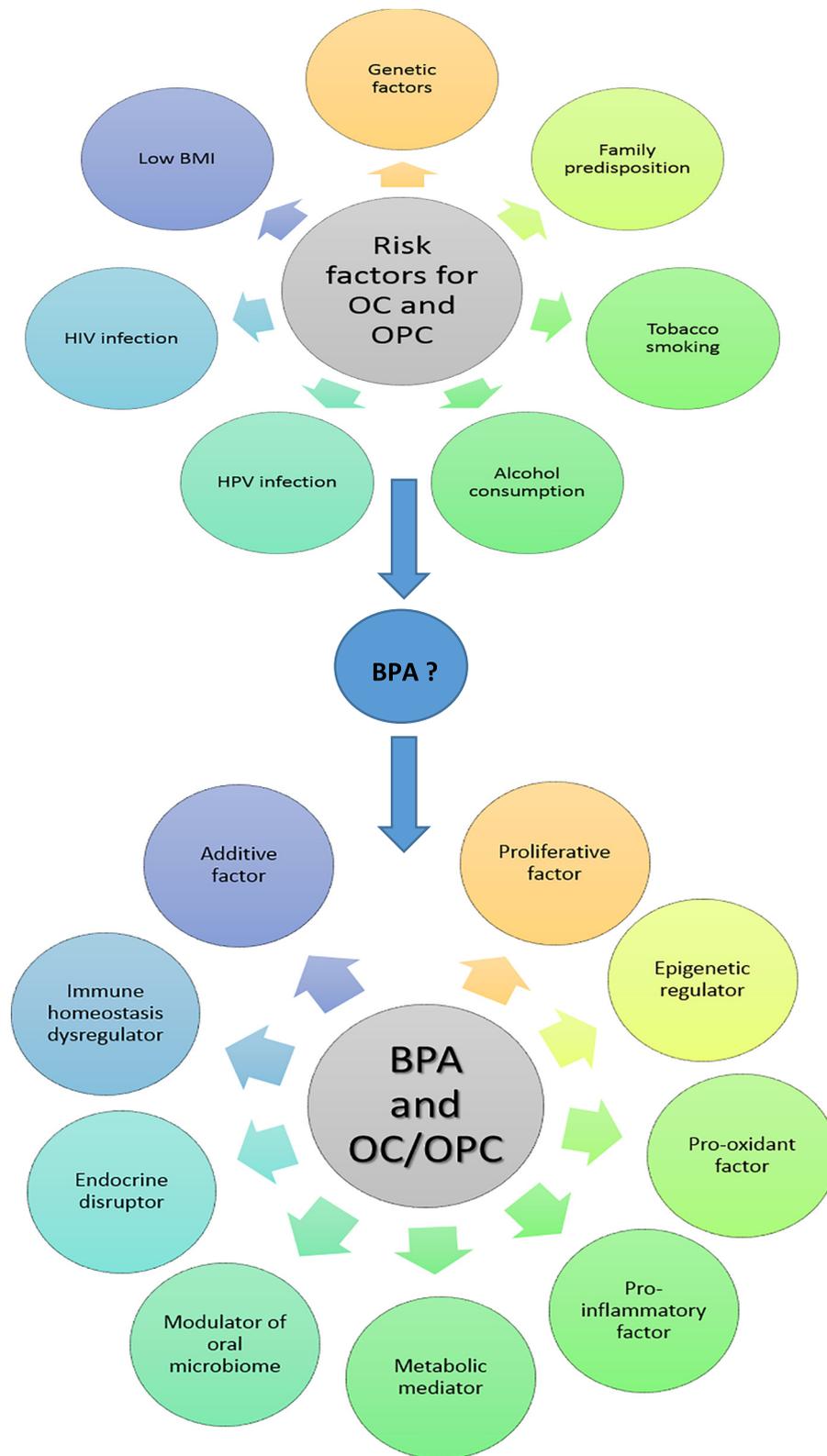


Fig. 3. Risk factors for oral and oropharyngeal cancers and potential mechanisms linking BPA to oral and oropharyngeal cancer.

with OC progression. In particular, increased lipid peroxidation products such as malondialdehyde and nitric oxide products as well as decreased enzymatic and non-enzymatic antioxidants were observed in patients with OC [72]. An inadequate antioxidant defense system may render the mucosal cells more prone to the genotoxic effects of ROS. Consequently, the intracellular space provides an ideal environment for DNA damage and cancer progression [73].

Multiple *in vivo* and *in vitro* studies have demonstrated the prooxidant actions of BPA, while its antioxidant properties have only been observed *in vitro* [74]. The genotoxicity caused by BPA exposure may be associated with the synthesis of ROS and phenoxyl radicals [74]. BPA exposure can change the recognition and repair of oxidatively-induced DNA damage via chromatin structure or alteration of DNA damage response and repair. The cytotoxic mechanism of BPA may be generated

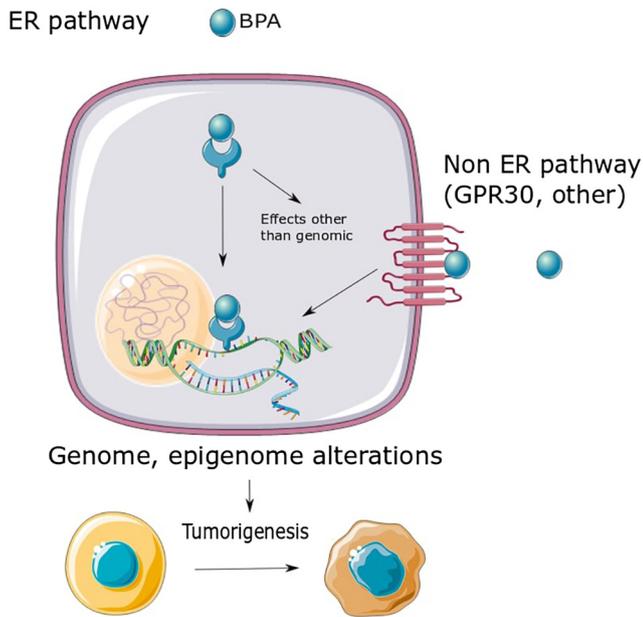


Fig. 4. BPA molecular mechanism of action. BPA is thought to exert its cancer promoting effects through the estrogen receptor signaling but also through alternative pathways such as GPR30, that possibly cause alterations in gene expression as well as other, non-genomic cellular events.

through the suppression of mitochondrial energy production and mitochondrial dysfunction. The BPA-induction of oxidative stress and inflammation response involves the activation of NF- κ B, MAPKs and PI3K/AKT pathways [74,75]. Upregulation of the aforementioned pathways has been associated with higher cell proliferation, increased synthesis of pro-survival proteins and metastatic potential in colorectal, prostate, breast and ovarian cells [74].

4.4. BPA as a Proinflammatory Factor Enabling Tumor Development

Chronic inflammation is present in multiple stages of carcinogenesis from the cellular transformation to the formation of tumoral milieu and metastasis [76]. Proinflammatory, proangiogenic and immunoregulatory cytokines are produced by squamous cell carcinomas and could play a role in the etiopathogenesis of Head and Neck Squamous Cell Carcinoma

HNSCC [77]. It has been observed that the concentrations of cytokines IL-6, IL-8, VEGF and acute phase proteins and TNF- α were higher in patients with HNSCC and squamous cell tonsil carcinoma respectively, in comparison to patients with benign squamous papilloma or control subjects [76,77]. Indeed, TNF- α exhibits a direct mutagenic effect generating DNA damage via ROS and inhibition of apoptosis mediated by the NF- κ B pathway [76].

In turn, BPA exposure induces immune cell-mediated inflammatory responses and increases the production of pro-inflammatory molecules, including TNF- α and IL-6 through the stimulation of MAPK signaling pathways [22]. The increased expression of cytokines and chemokines produced by macrophages and granulocytes indicates that BPA causes alterations in these cells. Simultaneously, BPA exposure may lead to a reduction of anti-inflammatory cytokines such as IL-10 [78].

4.5. BPA as a Dysregulator of Immune Homeostasis

HNSCC constitutes an immunosuppressive malignancy characterized by an elevated apoptosis rate of T lymphocytes, high levels of immunosuppressive cytokines, increased numbers of immunosuppressive regulatory T cells, defective function of remaining T lymphocytes and NK cells, as well as impaired antigen presenting mechanisms and maturation of dendritic cells [79].

BPA affects several signaling pathways related to immune responses and modifies various immune cells, including CD4⁺ T helper (T_h) lymphocytes, B lymphocytes, macrophages, mast cells, NK cells and dendritic cells. BPA-induced inflammatory responses are provoked primarily by the MAPK family and transcriptional factors like the AP-1, NF- κ B and STAT family. There are few data on BPA-mediated effects on T_h17 cells and it is not clear whether BPA causes Th1 or Th2 polarization [22]. Th1 and Th17 T cells produce pro-inflammatory cytokines, while Th2 or Treg cells generate regulatory or anti-inflammatory cytokines [63]. BPA reduces Treg cells, which are essential for immune cell balance, leading to an altered Th1/Th2 response [78]. Overall, BPA generates immune cell proliferation [63].

4.6. BPA as a Potential Modulator of Oral Microbiome

The oral microbiome is one of the most complex microbiomes harbored by the human body. The oral cavity hosts approximately 1000 species, amongst which are bacteria, fungi, viruses, protozoa and archaea. Particularly, bacteria may be involved in the development of OC [80].

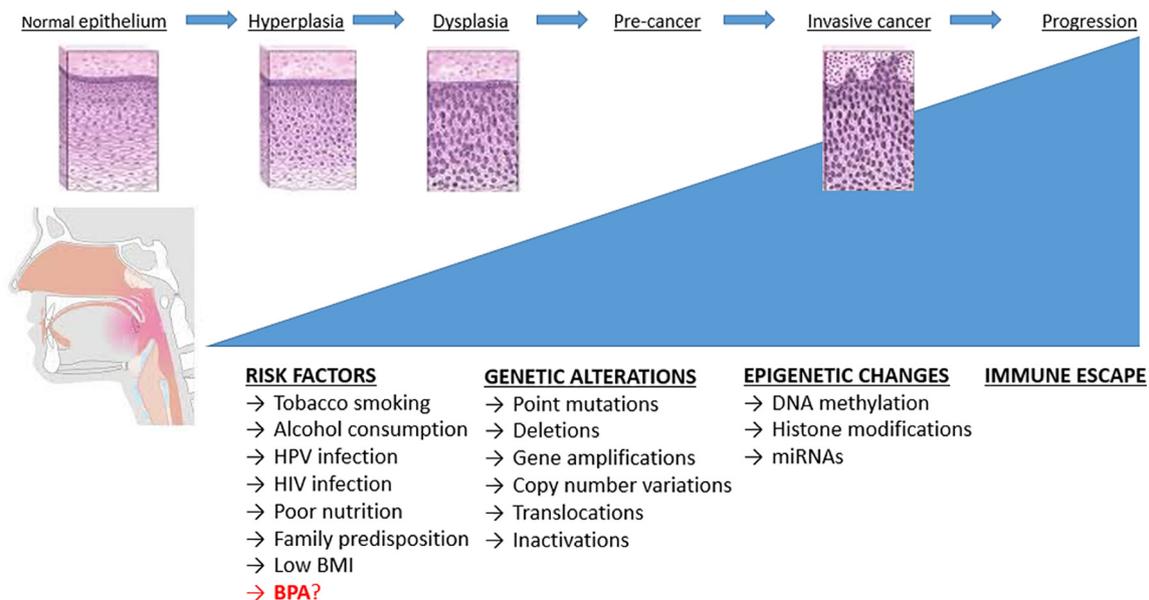


Fig. 5. Oral tumorigenesis is a complex process which includes several risk factors and steps as well as epigenetic and genetic modifications, resulting in genomic instability.

Due to its composition and function, the oral microbiome plays a role in mutational processes involved in OC, leading to different mutational patterns in OC [81]. In fact, bacteria involved in periodontal diseases, including *Porphyromonas gingivalis*, *Fusobacterium nucleatum* and *Prevotella intermedia*, are associated with OSCC. Such bacteria colonize the epithelium, generate carcinogens and provoke tumorigenesis, contribute to tumorigenesis in the initiated epithelium, metabolize pro-carcinogens and modulate the microenvironment leading to chronic inflammation [82].

So far, studies have shown that BPA exposure through the diet may affect the gut microbiome, though further studies are needed to investigate the effect of environmental contaminants on the gut microbiome in association with the development of disease. It is already known that the increase of *Helicobacteraceae* due to dietary BPA exposure may contribute to the pathogenesis of inflammatory bowel disease [83]. Perinatal BPA exposure may result in gut dysbiosis and modifications in gut metabolite profiles, leading to altered composition of the gut bacteria and decreased levels of beneficial bacterial metabolites, including short-chain fatty acids [4]. It would be interesting to explore the influence of BPA exposure in oral microbiome and oral disease states including OC.

4.7. BPA as an Endocrine Disruptor Chemical

BPA is both a xenoestrogen – since it is similar to DES, which is a synthetic estrogen – and an EDC [13]. In fact, BPA presents lower binding affinity for the classical nuclear receptors ER alpha and ER beta in comparison to estradiol. Upon administration, BPA acts as an estrogen when the endogenous estrogen levels are low. However, when it is administered in the presence of estradiol, it acts as an antiestrogen intervening with the action of estradiol [84].

Oral BPA exposure in rats presents adverse effects on buccal homeostasis, resulting in mouth dryness, thirst decrease, while chronic exposure to xenoestrogens may contribute to alterations in the structure of salivary glands, which are sensitive to steroid hormones [53].

4.8. BPA as a Metabolic Mediator Linking Insulin Resistance to Oral Cancer

Although obesity is considered to be a risk factor for various cancers, comprising endometrial, postmenopausal breast, colorectal, renal and esophageal (adenocarcinoma) cancers and hematological malignancies [85–87], case-control studies and pooled analyses have shown that BMI and weight are inversely associated with the risk of OC and OSCC [88,89]. This inverse correlation between BMI and OC/OSCC is debatable due to the weight loss caused by cancer cachexia and/or inflammation and the potential confounding effects of tobacco smoking and alcohol consumption [88]. The same phenomenon is presented in pancreatic and lung cancers, which manifest insulin resistance [50,90,91]. Insulin resistance, which can be seen in hyperadiposity and hypoadiposity, may be considered a risk factor for OC and OPC enhancing cell proliferation and preventing apoptosis [92,93]. Also, the role of adipose depots including neck and tongue fat needs to be investigated in the pathogenesis of OC, particularly oral tongue squamous carcinoma [50]. BPA has been associated with insulin resistance. Positive association between BPA, HOMA-IR and resistin as well as inverse association between BPA and adiponectin gene expression have been observed in obese children [94]. At low exposure concentrations, BPA may stimulate the mTOR pathway, which incorporates growth signals, including insulin and insulin-like growth factors, in order to enhance cell survival [63].

4.9. BPA as an Additive Factor in Oral Carcinogenesis

BPA may enhance in an additive manner the susceptibility of oral and oropharyngeal cells to subsequent exposures to risk factors associated with OC and OPC, such as tobacco smoking, alcohol consumption, HPV infection, HIV infection, poor nutrition, and family predisposition (Fig. 3). Oral tumorigenesis is a complex process which includes several risk factors

and steps as well as epigenetic and genetic modifications, resulting in genomic instability (Fig. 5).

5. Conclusions and Future Directions

Mechanistic, animal and epidemiologic studies have indicated that BPA exposure may raise cancer risk, particularly in hormone sensitive tissues [28,37] but also in other non-hormonal sensitive tissues, including the oral cavity and the oropharyngeal space. Based on experimental data in different cell types and models, BPA may target intracellular signals involved in oral cavity and oropharyngeal space cancer development through estrogen-dependent and independent pathways. BPA may lead to genetic, epigenetic, stress oxidative signaling and pro-inflammatory alterations, commonly observed also in OPC and OC [95]. BPA may alter oral microbiome in a similar way as it affects gut microbiome, leading to disturbed buccal and oropharyngeal cellular homeostasis. Future mechanistic studies will focus on analyzing the oncogenic mechanisms linking BPA to OC and OPC, that involve receptors or other cellular entities and the dose at which their effects take place. The bioinformatics analysis of the genomic, transcriptomic, proteomic and metabolomic data may also reveal additional pathogenetic aspects of OC and OPC following BPA exposure.

Animal studies evaluating the effects of early-life BPA exposure on genomic stability, epigenome changes and gene expression alterations in non-hormonal sensitive tissues including oral cavity and the oropharyngeal space are warranted. Also, there is need to explore the possible effects of BPA exposure on the metabolic diversity of oral microbiota in BPA-fed animals.

Large prospective and longitudinal population-based studies are required to determine whether BPA per se or in combination with other environmental exposures and metabolic factors may be associated with OC and OPC risk. Further multi-center studies will be needed to associate BPA with biomarkers of OC and OPC stemming from genomic, transcriptomic, proteomic, metabolomic and immunomic profiling. In addition to standard methods from statistics, machine learning approaches will be used to identify clinically meaningful subgroups of susceptible subjects. It will also be interesting to correlate urine and salivary BPA levels in OC and OPC subjects with 1) biomarkers of oxidative stress such as ROS, glutathione, TAS, homocysteine, malonyl-dialdehyde and oxidized LDL; 2) pro-inflammatory biomarkers such as hs-CRP, TNF- α , IL-6, IL-1 β , IL-10; 3) immunophenotype profile, including Tregs and T17 cells; 4) metabolic and lipid biomarkers, such as glucose, insulin, HOMA index, C-peptide, total cholesterol, triglycerides, LDL-cholesterol, and HDL-cholesterol; and 5) oral microbiome profile using 16S rRNA gene sequencing.

It will be imperative to discern the window time period for exposure and to characterize the susceptible populations at risk. Moreover, more research is needed with regard to BPA analogs, such as bisphenol-S (BPS), which have been increasing in manufacturing. Recent findings suggest that both BPA and BPS could be involved in obesity, metabolic processes and cancer [96]. Although their widespread use as alternatives for BPA, there is a lack of research on any associations with malignancies, including OC and OPC.

If a link between BPA exposure and OC and OPC risk exists, there will be theoretical and practical implications. From a practical perspective, future data may raise concerns about the deleterious impact of EDCs on non-hormonal associated-tissues. Fetal exposure to BPA could lead to long-term implications in the tumorigenesis of certain tissues. Interestingly, appropriate nutrient intake during pregnancy may restore epigenetic balance. Maternal diet enriched with methyl donors such as folic acid was shown to restrict DNA hypomethylation caused by BPA exposure [97]. Diet supplemented with antioxidants could potentially alleviate BPA-induced oxidative stress [73]. Also, this may encourage regulatory agencies to substitute these chemicals mainly from dental materials, food products and packages.

Potentially, there will be a need to monitor BPA levels in exposed individuals. Based on current literature, total urinary BPA concentration

(free and conjugated) in spot samples is considered a reliable tool for evaluating baseline BPA exposure across time reflecting all exposure sources. The best method for determining total urinary BPA levels is on-line solid-phase extraction coupled to isotope dilution high-performance liquid chromatography/tandem mass spectrometry [29,98].

Hence, it is not possible to rule out a potential role of BPA exposure in oral tissue carcinogenesis, especially knowing its potential to participate in other non-hormonal sensitive malignancies and to deregulate signaling pathways implicated in OC and OPC. Whilst understanding the link of BPA to OC and OPC might provide potential preventive targets, lifestyle amelioration including cessation of smoking and heavy alcohol consumption, adequate oral hygiene and a Mediterranean-based diet with consumption of fruits, vegetables and nuts, remains the most important component in reducing the risk of OC and OPC. Although the consequences of prolonged BPA and its derivatives exposure to OC and OPC risk are unknown, this perspective may provide insight into the association and open up new lines of investigation including non-hormonal associated malignancies [38].

Conflict of Interest Statement

No conflict of interest to disclose.

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Author Contributions

Rodopi Emfietzoglou performed literature search, wrote Sections 2, 3 and parts of Section 4 and created Table and Figures.

Nikolaos Spyrou performed literature search, wrote Section 1 and created Figures.

Christos S Mantzoros supervised, edited and reviewed the manuscript.

Maria Dalamaga conceived the theme, designed the review and its sections, performed literature search, wrote Sections 1, 4 and 5, edited and reviewed the manuscript.

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