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Translational aspects of the modern genetics in head and neck cancers

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Abstract: Oral cancer (OC) is one of the most recurrent cancers in the head and neck squamous cancer (SCCHN) category. Recently, the genome-wide association studies (GWAS) have gained growing interest in the scientific community. GWAS have identified several pathways involved in the interactions among general risk factors and genomic variants affecting SCCHN. This systematic overview aims to critically evaluate the latest data reported within the scientific literature. The aim was to investigate the impact of genetic aspects on SCCHN onset and prognosis, involving other clinical and systemic co-factors. PubMed, Google Scholar, and Cancer Genetics Web databases have been systematically investigated for original articles published in the last two years, reporting studies on the main queries addressed in this work. This review also comparatively describes the impact of environmental and pathological co-factors in different types of cancers, clarifying and updating the role of genetic factors in SCCHN onset and development. The main outcomes reported may be helpful to drive clinicians towards their clinical evaluations for the most appropriate therapeutic approach in SCCHN.

Introduction

Many genetic and environmental factors play specific role in increasing the risk of developing cancer. Nevertheless, not all people who are exposed to carcinogens or who have other risk factors will develop cancer. In fact, there are numerous pathways that work in the early stages, before the clinical onset. It is well known that genetics has a strong impact on several human diseases; however, several other factors influence the risk in developing oral cancers: tobacco smoke contains carcinogens that substantially increase the risk of developing cancer of the mouth. Furthermore, foods and other substances introduced with the diet can increase the risk of oral cancer: alcohol consumption is correlated with a higher risk of developing head and neck cancer (Huber and Tantiwongkosi, 2014; Kumar *et al.*, 2016; Siegel *et al.*, 2016).

Cancers that develop in the oral cavity encompass multiple anatomic sites, including the tongue, the gums, the lips, the mouth floor, hard palate, and retromolar trigone. Cancer of the oropharyngeal space located between the hyoid bone and the soft palate includes the tonsillar region, base of the tongue, soft palate and uvula and the posterior and lateral pharyngeal walls. All of these sites are considered at risk of developing OSCC of the head and neck (SCCHN) (Huber and Tantiwongkosi, 2014). Although oral cancer (OC) and oral and oropharyngeal cancer (OPC) possess different behaviour and prognosis, both of them are characterised by atypical squamous epithelial cells, and are termed oral squamous cells carcinoma (OSCC) (Kumar *et al.*, 2016; Siegel *et al.*, 2016). The worldwide incidence of OC increases with age and depends on the patient's gender; it has been determined that the average age for OC diagnosis is 64 years old, while 95 percent of OC diagnoses occur after 40 years (Mignogna *et al.*, 2004; Abram *et al.*, 2012; Bray *et al.*, 2018). More than 600,000 new oral cavity cancer cases have been estimated to occur each year, and the majority of cases are typically recorded in south-central Asian countries (Conway *et al.*, 2018).

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OPCs have major and well-known risk factors, such as alcohol consumption, HPV infection and cigarette smoking. Within this landscape, the role of genetic factors and the influence of environmental compounds are increasingly attracting interest from the scientific community (Curry *et al.*, 2014; Li *et al.*, 2018). Recent studies have revealed a specific association between oral cell mutations and OC onset. For example, patients with Fanconi anaemia with mutations in genes essential to the DNA repair process possess a higher risk of developing OC with respect to the general population (Yardimci *et al.*, 2014). Patients with dyskeratosis congenita syndrome also carry a higher risk of developing OC, which can initiate from their childhood. Moreover, patients with Li-Fraumeni syndrome are also predisposed to early-onset of OC (Yardimci *et al.*, 2014).

The pathogenesis of OC recognizes different phases that can be influenced by several endogenous and exogenous factors which affect the clinical behaviour of OC (Ranganathan and Kavitha, 2019). Therapeutic choices for OC mainly depend on the tumour staging at its first diagnosis (Gődény, 2014; Marur and Forastiere, 2016). Moreover, the prognosis typically depends on the development of metastasis in the neck or other lymphatic organs (Huang, 2013; Marcazzan *et al.*, 2018). Currently, the most effective therapy of OC is surgery; however, the choice may be between surgery and radiation therapy. In those cases, characterised by severe clinical progression, the surgeons may decide to treat OC with surgery combined with radiation therapy. Chemotherapy can also be helpful in several types of OC (Yoshida *et al.*, 2020): it can be used after the primary surgery, as adjuvant therapy, or as a preventive treatment, functioning as a neo-adjuvant therapy (Warnakulasuriya and Khan, 2017; Kim and Li, 2019).

Recently, new drugs have been introduced in OC therapy based on selective mechanisms, defined as target therapy (Gillison *et al.*, 2019b). The use of targeted therapy potentially decreases the toxicity of drugs and increases their selectivity, aiming to improve the effectiveness of treatments. In this context, there has been recent approval for using a monoclonal antibody against the epidermal growth factor receptor (EGFR) called cetuximab, either alone or in combination with radiotherapy and chemotherapy (Kioi, 2017). Other targeted agents under experimental investigation for their efficacy against OC are vascular endothelial growth factor receptor (VEGFR) inhibitors, EGFR tyrosine kinase inhibitors, and a range of other inhibitors acting on several key targets, including immune checkpoints (Strange *et al.*, 2001).

Genetic abnormalities in SCCHN have been widely studied, and frequent alterations are significantly associated with aggressive forms of SCCHN. Since OC often results in malignant prognosis (Abram *et al.*, 2012), there is an urgency to identify novel reliable and early biomarkers: and the genetic landscape highly impacts OC onset and prognosis. Thus, a clear overview of the most significant interactions between these two topics may be strategic in identifying prognostic patient survival markers to enable the selection of the most appropriate treatment or for the development of new targeted oncological therapies. This systematic overview aims to critically evaluate the latest data reported within the scientific literature. The aim was to investigate the impact of genetic aspects on SCCHN onset and prognosis, also involving other clinical and systemic co-factors.

Experimental Section

Protocol and registration

This systematic review is part of the project "*Calabrian Genetics*," and it has been registered (MH2020_TRI_03_GENE); the data have been archived in the data repository.

Eligibility criteria

The purpose of this systematic review was to critically analyse the most impacting and updated publications, published up until May 2020 on PubMed (https://pubmed.ncbi.nlm.nih.gov/), Google Scholar (https://scholar.google.com/), and Cancer Genetics Web databases (http://www.cancerindex.org/geneweb/). The keywords used were: "genetic" and "oral cancer and oropharyngeal cancer" and/or their synonyms. The first critical analysis was on the title and abstract of each item. The full texts of relevant studies were selected and underwent a more in-depth evaluation. A crosscheck of all the references included in all the selected articles was also evaluated to find other potentially critical studies not initially included in our search strategy.

Study selection

Full-text articles were selected based on a robust correlation between genetic factors and oral cancer onset. Moreover, we included articles reporting new concepts on genetic variability and its impact on diagnosis/prognosis in oral cancer. Finally, we searched for genetic variability combined with specific exogenous and environment co-factors in oral cancer onset/severity. We excluded studies that were: outside our topic, duplicate studies/data, book chapters, reviews, editorials, oral presentations, poster presentations, technical notes and/or retracted papers. Articles included in our review were written only in the English language.

Results

Study selection

Our initial search identified 1528 articles from PubMed, Google Scholar, and Cancer Genetics Web database. After removing duplicates and articles that did not contain appropriate information regarding the topic, 300 unique citations remained for our screening based on abstract and title. After abstract, title screening and full-text screening, 60 original research studies were identified, containing relevant information for review. Of these, only 14 articles were selected as being the most relevant according to the provision of statistically significant data obtained, which related to the aim of our review. A detailed PRISMA flowchart of the article's selection process is shown in Fig. 1.

Data processing

We reported information, such as year of publication, first author, sample size, investigated genes, and results, from each study: these data are summarized in Table 1. We utilized the preferred reporting items for systematic reviews (PRISMA) statement checklist for this systematic review (Fig. 1). Data extraction from reports was obtained independently from different investigators. The funding source was not used in the data extraction and analysis. To

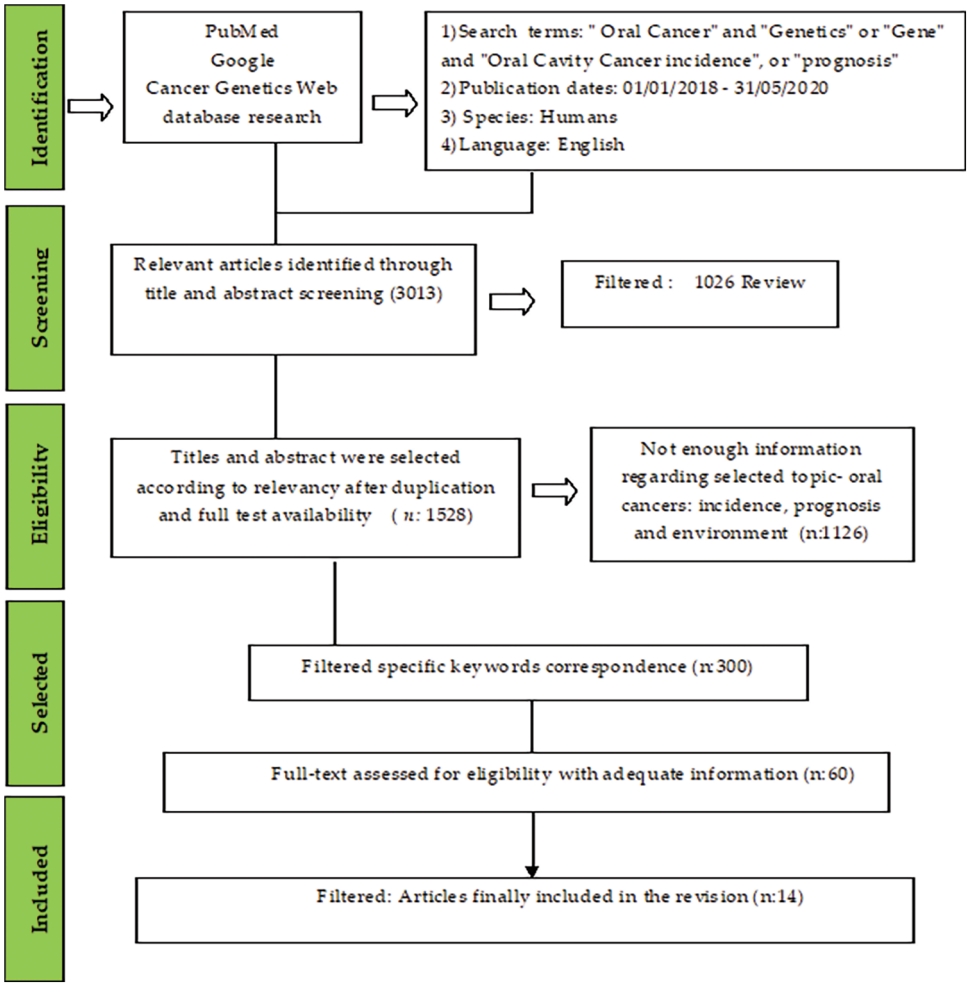

FIGURE 1. PRISMA flow diagram showing study selection.

TABLE 1

OSCC of the head and neck (SCCHN)

Year	Author	Subjects (n)	Sample	Gene	Result	*P*-value
2020	(Yadav *et al.*, 2020)	445 OC (192 RAN- 253 RAN+TOB)	PB	*GSTP1*	rs1695 (A > G) AA	*P = 0.0002*
2020	(Shete *et al.*, 2020)	631 OC	PB	*CLPM1L HLA-DQB1*	rs2447853 rs3135001	*P < 0.001*
2019	(Goud *et al.*, 2019)	41 OSCC of head and neck cancer including OPC	TS	*IL10* *A1082G*	No significant	*P = 1.024*
2019	(Gillison *et al.*, 2019a)	149 HPV^{+} OSCC	TS	*APOBEC*	significant	*P = 0.006*
2019	(Sharma *et al.*, 2019)	300 OC	PB	*TLR 9* *TLR 4*	TLR 9 (−1486 T/C) TLR 4 (+896 A/G)	*P = 0.0001*
2019	(Huang *et al.*, 2019)	452 OSCC	PB	*CXCR4* *SDF-1*	CXCR4 C > T	*P = 0.033*
2019	(Muraki *et al.*, 2019)	89 OSCC	TS	*KLF4*	significant	*P = 0.004*
2019	(Nigam *et al.*, 2019)	250 OC	TS	*CYP1A1*	A4889G	*P = 0.025*
2019	(Yeh *et al.*, 2019)	865 OSCC	PB	*PTX3*	rs3816527	*P = 0.001*
2019	(Lin *et al.*, 2019)	741 OC	PB	*CK1ε*	rs165745	*P = 0.029*
2018	(Daigo *et al.*, 2018)	99 OC	TS	*KIF11*	significant	*P = 0.034*
2018	(Avci *et al.*, 2018)	111 OSCC	PB	*XPG XPD*	rs13181	*P = 0.019*
2018	(Su *et al.*, 2018)	1044 OSCC	PB	*eNOS*	rs2070744 (TC+CC)	*P = 0.019*

Note: Details of the selected articles used in our analysis. Legend/abbreviations: Peripheral Blood (PB), Tissues Samples (TS). To avoid operators' bias, each data extraction and analysis was performed 3 times by two different authors expert in data mining.

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Crosstalk between genetics and epidemiology in oral cancer pathogenesis

The glutathione S-transferases (GSTs) family enzymes are crucial in cellular resistance mechanisms (Huang *et al.*, 2008) and cancer patient response to treatments. GTSs play a significant role in detoxification processes by catalysing the conjugation of the reduced form of glutathione (GSH) to xenobiotic substrates (Yadav *et al.*, 2020). These enzymes are encoded by polymorphic genes comprising five classes, including alpha, Pi, Mu, Theta, and Zeta. A common and relatively widespread single nucleotide polymorphism (SNP) of the glutathione-S-transferase P1 (*GSTP1*) gene, which is a member of the *GST* family, has been associated with a significant reduction in enzyme activity. The SNP rs1695 (I105V) is characterised by a single A > G substitution in nucleotide 313 and determines an alanine to valine substitution. This substitution decreases the enzymatic activity of GSTP1 and appears to be a susceptibility factor for OC development. Yadav *et al.* (2020) investigated this polymorphism by genotyping 444 controls and 445 cases of OC in the Indian population (Warnakulasuriya *et al.*, 2010). Data indicated that patients who had the *GSTP1* AA-genotype had a high association with the onset of OC.

Tobacco smoking is a well-known and preventable risk factor for OC, especially in Asian populations (Leichsenring *et al.*, 2006). The role of the AA-genotype is correlated with the habits of smoking and chewing tobacco (Guengerich, 2008), in the presence of numerous smoke-related DNA lesions, this genotype is frequently associated with lower c-Jun phosphorylation and reduced apoptosis rate in submucosal cells, thus predisposing these individuals to increased risk of developing OC.

Also, CYP1A1, a member of the cytochrome P450 superfamily, catalyses several reactions, including those involved in drug metabolisms. These enzymes are also involved in several metabolic processes, which result in pro-carcinogens becoming active carcinogens (Nigam *et al.*, 2019). Analyses within the population of tobacco consumers have demonstrated a significant correlation between *CYP1A1* polymorphisms and increased incidence of OC (Su *et al.*, 2018).

Moreover, smoking habit and increased risk of OC have also been correlated with endothelial nitric oxide synthase (*eNOS*) gene polymorphisms in the Taiwanese male population (Choudhari *et al.*, 2013). Current knowledge demonstrates that nitric oxide (NO) is involved in carcinogenesis and cancer progression and that the effect of NO on cancer cells is related to the interaction involving *eNOS* expression levels, cell type, genetic background, and tumour microenvironment (Teicher and Fricker, 2010). With these premises, two SNPs of the *eNOS* gene, known as rs2070744 (−786 T > C) and rs1799983 (894 G > T), were genotyped in 1044 patients with OC and 1200 controls. Results showed that patients carrying the TC genotype exhibited an increased risk of developing OC in Stage III/IV than those carrying the TT genotype. Furthermore, these two SNPs located in the *eNOS* gene combined with cigarette smoking was strongly associated with the risk of malignant transformation.

The chemokine stromal cell-derived factor1 (SDF1) and its receptor C-X-C chemokine receptor type 4 (CXCR4) regulate the homeostasis of immune cells. Studies have recently demonstrated that *CXCR4/SDF1* interaction can regulate numerous crucial events in cancer onset and behaviour (Huang *et al.*, 2019). Huang *et al.* analysed the genotypes of *SDF-1* and *CXCR4* in OC patients and studied the association between specific polymorphisms in these genes and the risk of developing OC (Daigo *et al.*, 2018). Patients with SNPs in *SDF-1/CXCR4* showed a higher risk of OC onset. Moreover, the C/T+T/T genotypes were reported to be responsible for an increased OC risk, specifically in smokers or heavy alcohol consumers with respect to patients carrying the C/C genotype. The authors consequently demonstrated that *CXCR4* C > T genotype provided a genetic marker of OC susceptibility.

Daigo *et al.* (2018) performed a interesting comparative study using SCCHN and normal tongue epithelial tissue microarray analysis in solid tumours combined with genome-wide gene expression profiling (Jungwirth *et al.*, 2019). The authors demonstrated that the motor protein Kinesin Family Member 11 (KIF11), involved in numerous types of spindle dynamics such as centrosome separation, chromosome positioning, and tumour genesis, is expressed in most OC tissues (Shete *et al.*, 2020). Conversely, KIF11 was barely detected in healthy tissues and has often been correlated with a poor prognosis in OC patients.

Recently, a GWAS carried out on Caucasian patients showed that alterations affecting several chromosomal regions were able to increase, in some cases, the risk of developing OC. In particular, Shete *et al.* (2020) reported a GWAS involving 631 OC patients, which detected two loci significantly associated with OC. The first gene locus was on chromosome 6p21.32, and the second was located on chromosome 5p15.33. Other GWASs were aimed at exploring modifications of genes related to DNA repair pathways: as these genes have been studied as a potential risk factor for OC, as reported by Avci *et al.* (2018). Indeed, the relationship between the xeroderma pigmentosum complementation group G and D *(XPG* and *XPD*) gene variants in DNA repair pathways was investigated in 111 patients. Consequently, the Lys751Gln SNP in the *XPD* gene was found to play a critical role in OC development.

Commonly, some genotypes of the human papillomavirus (HPV) are associated with OC. Two recent studies by Gillison *et al.* (2019a) and Sharma *et al.* (2019) investigated the most critical genetic alterations which correlate with HPV patients developing OSCC of the head and neck (SCCHN). Using a comprehensive genomic analysis, Gillison compared 335 HPV-negative and 149 HPV-positive OC tumours and healthy tissues (Siegel *et al.*, 2016; Gillison *et al.*, 2019a). They observed an association between apolipoprotein B mRNA editing catalytic polypeptide-like (APOBEC) cytosine deaminase editing and overall mutation burden in HPV-positive OC patients, likely associated with an anti-viral immunological response.

Conversely, HPV-negative OC patients reported T > C substitutions in the sequence "5′-ATN-3′", which frequently correlated with exposure to tobacco smoke.

The role of Toll-like receptor (TLR) genotypes was evaluated by Sharma and colleagues (Sharma *et al.*, 2019). They analysed pre-cancerous or cancerous oral tissues and investigated correlations with HPV/EBV co-infection in the Indian population. Notably, the TT *vs.* CT + CC genotypes of *TLR-9* were compared: TT genotypes appeared to have a wider risk for the development of OC from pre-cancerous lesions compared with controls; and there was an increased tendency for this association in HPV+/EBV+ patients, as the co-infection was also able to enhance pathogenesis induced by tobacco chewing and smoking. The current literature body also provides evidence for the role of long pentraxin 3 (*PTX3*) SNPs in OC risk. By evaluating the effect of *PTX3* gene polymorphisms on overall OC susceptibility, Yeh *et al.* (2019) found the SNPs of rs2305619, rs1840680, rs2120243 and rs3816527 in the *PTX3* gene in 865 OC patients affected disease pathogenesis. In particular, the rs3816527 variation in smokers was correlated with the development of aggressive cancers, with an increased risk of developing metastases. Also, the casein kinase 1 epsilon (*CK1ε*) gene is known to play a key role in several cancers, including OC (Lin *et al.*, 2019). In this context, the SNPs of rs135764, rs135745, rs2075984 and rs1997644 on *CK1ε* gene were assessed in 741 OC patients (Lin *et al.*, 2019). Data demonstrated that the GC variant of *CK1ε* gene SNP rs135745 showed a significantly higher risk for OC. Notably, there are contrasting reports in the literature. Indeed, published data (Hussain *et al.*, 2016) has indicated the *IL10* A1082G gene polymorphism was not associated with a higher incidence of OSCC in Malaysian patients, as was previously reported (Goud *et al.*, 2019).

Discussion

Cancer has a multifactorial etiopathogenesis in which genetic factors play a crucial role. The stochastic onset of genetic mutations appears to be usually unable to cause cancer alone; however, the combination of both genetic and environmental co-factors can contribute to cancer development due to their interaction. Arguably, the most critical genetic mutations involve genes that regulate DNA repair, cell cycle, cell apoptosis, and other biological activities associated with neoplastic behaviour (Coyle *et al.*, 2017). The risk factors in OC patients are strongly correlated with specific genetic alterations, and knowledge of these genetic variations will be important in diagnostic, prognostic, and other screening purposes.

Furthermore, these variations can also be used for targeted therapies of OC (Strange *et al.*, 2001; Huang *et al.*, 2008; Huang, 2013; Gődény, 2014; Marur and Forastiere, 2016; Kioi, 2017; Warnakulasuriya and Khan, 2017; Marcazzan *et al.*, 2018; Gillison *et al.*, 2019b; Kim and Li, 2019; Yoshida *et al.*, 2020). Early identification of those cancers which develop after specific genetic mutations may provide significant benefit for the healthcare system, to enable a reduction in cancer incidence and prevalence, as well as in decreasing the severity of the symptomatology of patients (Teicher and Fricker, 2010; Jungwirth *et al.*, 2019; Muraki *et al.*, 2019; Nigam *et al.*, 2019). This critical review investigated the relationship between gene involvement and OC incidence, progression, and fate. The knowledge of the mutual interactions among co-factors influencing OC is crucial from several clinical points of view (Guengerich, 2008; Conde-Pueyo *et al.*, 2009; Coyle *et al.*, 2017). Although the effective contribution by single factors on OC onset may still be considered unclear and variable, it must be considered fundamental that the risk of developing OC is frequently determined by complex crosstalk among genetic and environmental factors (Strange *et al.*, 2001; Leichsenring *et al.*, 2006; Guengerich, 2008; Huang *et al.*, 2008; Teicher and Fricker, 2010; Warnakulasuriya *et al.*, 2010; Choudhari *et al.*, 2013; Huang, 2013; Gődény, 2014; Marur and Forastiere, 2016; Kioi, 2017; Warnakulasuriya and Khan, 2017; Daigo *et al.*, 2018; Marcazzan *et al.*, 2018; Su *et al.*, 2018; Gillison *et al.*, 2019b; Huang *et al.*, 2019; Kim and Li, 2019; Nigam *et al.*, 2019; Shete *et al.*, 2020; Yadav *et al.*, 2020; Yoshida *et al.*, 2020). Indeed, many well-established environmental and lifestyle risk factors affect OC development (Kumar *et al.*, 2016): together, they may be considered the causes of about 80% of OC deaths (Conde-Pueyo *et al.*, 2009; Hussain *et al.*, 2016; Coyle *et al.*, 2017; Goud *et al.*, 2019). In addition to the risk factors commonly associated with OC, a specific role of genetic alterations has been recently highlighted, along with the interactions with endogenous and exogenous causes (Strange *et al.*, 2001; Huang, 2013; Gődény, 2014; Marur and Forastiere, 2016; Kioi, 2017; Warnakulasuriya and Khan, 2017; Marcazzan *et al.*, 2018; Gillison *et al.*, 2019b; Kim and Li, 2019; Ranganathan and Kavitha, 2019; Yoshida *et al.*, 2020). GWAS and next-generation sequencing (NGS) studies have begun to clarify the many genetic variations that contribute to the overall incidence of many cancers, included OC (Johansson *et al.*, 2012; Sharma *et al.*, 2017). These new techniques allow analysis in several human populations and significantly improve our knowledge based on OC biology. The early diagnosis of OC will benefit from a better knowledge of the biological phenomena involved. This information may translate to significantly improving the patient's quality of life and increase the overall survival to OC.

Early OC detection is a key aim of scientific and clinical research in oncology. Due to GWAS investigations, alterations of *TP53*, *CDKN2A*, and *PIK3CA* genes have been recently discovered in OC patients (Leemans *et al.*, 2011), and several new potential biomarkers have been hypothesized to be worthy of further investigation (Collins *et al.*, 2013). Initially, Boyle *et al.* (1993) demonstrated an increase of *TP53* mutations in patients with invasive lesions of HNSCC; subsequently, other authors (Qin *et al.*, 1999; Gissi *et al.*, 2015) have elucidated that *TP53* mutations found in erythroplakia were correlated with the increase in OC onset (van Ginkel *et al.*, 2016). Moreover, in a study conducted by Menicagli *et al.* (2016), which analysed the mechanisms involved in genetic alterations and promotion of OC, 14 new genes were discovered as being involved in the development of this tumour (Gissi *et al.*, 2015; Menicagli *et al.*, 2016; Van Ginkel *et al.*, 2016). Arguably, the most significant finding reported by Menicagli was that two

specific genetic alterations were considered pathognomonic in the highest percentage of OC patients: this involved the genes of *TP53* and *CDKN2A* (Menicagli *et al*., 2016). Several studies have also evaluated the correlation between *GST* family member polymorphisms in OC (Sikdar *et al*., 2004). New data reported by Yadav *et al*. (2020) confirmed such association and indicated that incidence increased with certain lifestyle habits.

A strong correlation between *CCND1*, *JUN*, and *SPP1* genes and lymph node metastasis in OC has already been observed (Zhang *et al*., 2018): the new data summarized in this review highlighted how the *PTX3* gene appears to be involved in metastasis in OC (Su *et al*., 2018). Moreover, alterations of DNA observed in OC patients by Cervigne *et al*. (2014) have been further confirmed by Shete *et al*. (2020).

In our critical review, the analysis of the scientific literature has allowed the comparison of different diagnostic and therapeutic pathways, related to several OC. Indeed, new therapeutic strategies based on targeted therapy, including gene therapies, have been considered the gold standard, as is reported in several clinical trials (Li and Zhang, 2015). Currently, targeted therapies developed and applied in OC patients involve inhibitors of cell surface signalling receptors of EGFR (gefitinib, erlotinib, and cetuximab) and cellular signalling pathways and/or immune checkpoints. Future therapies are currently under development: for example, some novel gene disruption therapies, or gene addition therapies, are combined with specific epigenetic modification therapy along with traditional surgical therapy and radiotherapy (Nandini *et al*., 2020). A thorough knowledge of new genetic biomarkers in OC will aid clinicians in choosing the most appropriate treatment strategy (Inchingolo *et al*., 2011). Recently, stem cell-based therapies have also been proposed (Ballini *et al*., 2017; Marrelli *et al*., 2018; Tatullo, 2018; Tatullo *et al*., 2019c; Tatullo and Gandolfi, 2021); however, several issues still affect the use of this type of biological therapy. Early detection and diagnosis of suspicious lesions will continue to however be essential to enable enhanced treatment efficacy (Inchingolo *et al*., 2012; Aulino *et al*., 2015; Tatullo *et al*., 2018).

Our review supports findings that alterations in genes involved in tumour suppressors play a crucial role in the onset and severity of degenerative processes involving somatic cells. Indeed, such alterations may trigger other genes involved in cancer development. While these genes typically carry alterations in about 90% of cases of OC; notably, these genes may also be involved in the onset of other cancers, including colon, breast, and leukaemia. Thus, the genetic factors have a pivotal role in several pathogenesis; it is also important to remark that other factors play a pathogenetic role, such as the local inflammation, which negatively affects the ability of tissues to self-regenerate/repair. Specifically, chronic inflammations related to micro-/nano-particles released from medical devices or implants used in dental treatments have been related to this pathway (Bressan *et al*., 2019).

Significantly, the diagnosis of malignancies before metastasis will likely reduce morbidity and improve the patient's quality of life and overall survival. Interestingly, exosomes are micro- and nano-vesicles released by cancer stem cells (CSCs) and these may have a role in the development of metastatic cancers; promising studies have also hypothesized that such vesicles can be managed and stored to be used for diagnosis and prognosis in different diseases models (Codispoti *et al*., 2018; Tatullo *et al*., 2019a; Tatullo *et al*., 2020). Similarly, new technologies have been investigated to support early diagnosis using innovative smart biomaterials, such as the Graphene; recently, other allotropic 2D biomaterials have been also studied for their potential interest in biomedical applications, such as the Phosphorene and the Borophene. The main applications of these materials is in probes and devices able to register biometric data, to be used for early diagnosis and to accurately follow the prognosis of complex oncological therapies (Tatullo *et al*., 2019b; Tatullo *et al*., 2019d).

Systematically analysing OC susceptibility to specific genes provides an attractive approach. However, an in-depth and fundamental understanding of the mechanisms and pathways involved in cancer development is essential. Individuals undergoing genetic testing for OC should be fully informed regarding the potential implications of such information, and both patients and surgeons should discuss appropriate therapeutic pathways.

Conclusions

Complex crosstalk between genetic and environmental factors, microbiological compounds, and patient's biology, drives the onset of SCCHN. Although lifestyle choices, such as tobacco smoking, or alcohol consumption, have been demonstrated to be severe risk factors for oral cancer, genetics also play a primary role in its development. Individuals carrying specific genetic alterations have been linked to a higher risk of developing this class of diseases. In this landscape, most oral pathologists routinely screen for oral cancer during a specialist visit: the knowledge of co-factors, signs and genetic alterations playing a role in OC developments, is well reported in this critical overview, and is fundamental to saving human lives. This overview contributes to understanding the role of genetics in SCCHN onset and severity: this knowledge may improve the awareness and use of predictive genetic tests based on well-characterised markers to preventively screen patients with a family history of SCCHN. An exciting strategy raised by this review is to combine and integrate data relating to genetic alterations and the primary outcomes after traditional therapies in SCCHN patients. This approach could improve the knowledge on the efficacy of specific drugs in specific genetic landscapes. In conclusion, taking into consideration the limitations related to the specific data involved in our study, our overview has reported the most updated summary of genetic alterations and their clinical impact on SCCHN patients. This information may have utility in driving research towards the development of improved diagnostic and therapeutic strategies in the future.

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