Review

Single Nucleotide Polymorphisms as a Biomarker in the Assessment of Oral Mucositis in Head and Neck Cancer Patients: A Systematic Review

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Single Nucleotide Polymorphisms as a Biomarker in the Assessment of Oral Mucositis in Head and Neck Cancer Patients: A Systematic Review

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Abstract: Single Nucleotide Polymorphisms (SNPs) are the most common type of genetic variation found in individual's DNA sequences. SNPs can occur in both coding and non-coding regions of the genome and can affect gene expression, protein function, and disease susceptibility. In this systematic review we evaluate the influence of SNPs as a biomarker in the assessment of oral mucositis (OM) in head and neck cancer (HNC) patients. The study selection process involved screening 66 articles from different platforms, and after removing duplicates and excluding irrelevant articles, 23 articles were included for full-text evaluation. The main characteristics and findings of the selected articles are presented and discussed. We conclude that SNPs can be used as a reliable biomarker for the assessment of OM in HNC patients, and further research is needed to explore the potential of SNPs in personalized medicine for HNC treatment.

Keywords: Head and neck cancer; mucositis; chemoradiotherapy; SNPs

INTRODUCTION

Head and neck cancer (HNC) represents a heterogeneous group of malignancies, located in an anatomical region containing delicate structures with close relationships to each other and involved in critical functions such as feeding and breathing. In addition, the natural history of disease and the adverse effects of treatment can directly impact the patient's appearance, verbal expression, and social interaction. It originates from epithelial or glandular tissue lining the aero-digestive tract and it can involve the oral cavity, pharynx, nasal cavity, larynx, thyroid, and salivary glands.

HNC is a relatively common cancer worldwide, with approximately 950,000 new cases and 470,000 deaths per year across all subsites, and the global incidence is estimated to have increased by 34 % by 2030 (Sung et al., 2021).

Until the early 1990s, local curative treatment was primarily based on surgery with or without postoperative radiotherapy (RT). Later on, several publications started to demonstrate the possibility of organ preservation without loss of overall survival in selected groups of patients treated with concomitant chemoradiation (CRT) making combined treatment a viable option (Wolf et al., 1991; Pignon et al., 2009). However, conservative treatment with concurrent chemotherapy (CT) has altered and intensified some of the already known toxicity patterns of RT (Elting et al., 2007).

Mucositis is a frequent and acute complication, occurring regularly in patients receiving CRT. The patient may develop, to varying degrees, dysphagia, odynophagia, dehydration, weight loss, and it is often necessary to temporarily interrupt RT or reduce the dose of CT, affecting outcomes and increasing frequency, duration, and costs of hospitalization and antibiotic

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therapy (Elting et al., 2007). Worsening severity of mucositis is related to declining levels of quality of life (Murphy et al., 2007).

Classically, mucositis was described exclusively as a direct and local effect of radiation damage to the DNA of basal layer cells, influencing their multiplication and replacement of mucosal surface cells. Radiation-induced mucositis was classically recognized as an "outside-in" process. The concept of mucosal injury as a biological and multifactorial process is relatively new.

In 2004, Sonis et al. published a study describing aspects of the development of mucositis as a dynamic process involving the activation of different pathways, described in a model of distinct phases (Sonis, 2004). The complexity of its pathogenesis, with description of distinct biological pathways and associated systemic factors, has been increasingly explored (Villa & Sonis, 2015).

Previous data have reported a possible association between genetic polymorphisms in different pathways and the development of mucositis, acting as potential biomarkers of severity (Normando et al., 2017a). The most common type of polymorphism is one involving a single nucleotide, called single nucleotide polymorphism (SNP).

The early identification, through the analysis of molecular aspects of patients who possibly have a higher chance of developing mucositis, as well as its intensity, represents a promising area and the chance of a new approach to this frequent complication.

The identification of SNPs in genes linked to biological pathways, allows new targeted treatments to be developed to act in early stages, inhibiting molecules or pathways that were previously unknown, opening up possibilities for new and personalized therapies, as well as early implementation of preventive measures in a specific patient who is more likely to develop a serious adverse effect or not. The purpose of this systematic review is to identify studies that evaluated SNPs in different pathways as biomarkers of mucositis intensity.

METHODS:

This systematic review was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklist.

Eligibility criteria:

Articles were included that addressed the relationship between SNPs in different biological pathways as biomarkers of the severity of oral mucositis (OM) in HNC patients receiving RT or CRT. The treatments had to be curative and RT could be used as a radical or post-operative treatment.

Articles were excluded because of the following reasons: evaluated patients with other types of cancer; HNC treatment without CRT; no correlation of the SNP with the severity of mucositis; reviews, letters, personal opinions, book chapters, and conference abstracts; association between biomarkers and OM in experimental studies (clinical trials, *in vitro* or *in vivo* animal studies); and language restrictions.

Information sources and search strategies:

An exhaustive search was carried out in the main databases used as research tools - Pubmed, LILACS, Science Direct and Cochrane. Articles published between January 2009 and September 2022 were included for analysis. All duplicate articles were removed. In addition, the references of the included articles were reviewed to detect publications that were not identified in the search process.

Study selection and data collection process:

In the first phase, the articles were listed in the databases and all the titles and abstracts were reviewed by two independent authors (RC and HO), who made the primary selection. The second phase consisted of reading the full text and retrieving those that met the inclusion criteria.

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This stage was also carried out by the same two authors (RC and HO). In the event of disagreement, a third author (MK) decided whether or not to include the reference. The references of the articles were reviewed by the first author (RC).

For all the articles included, the following information was recorded: authors, year of publication, country, number of patients, RT dose, treatment modalities, pathways of the polymorphisms studied, type of study, and main conclusions.

Study Risk of Bias and Quality Assessment

The quality and possible sources of bias of the selected studies were assessed using the Newcastle Ottawa Scale (NOS) tool, specific for observational studies. Three quality parameters (selection, comparability, and results), divided into eight specific items, were assessed. Each item on the scale was scored out of one point, except comparability, which can be scored out of two points. The maximum for each study is nine, and references with less than five points are identified as representing a considerable risk of bias.

Two authors independently verified the parameters (RC and TL). A third author (HO) decided in case of disagreement

RESULTS:

Study Selection

After the terms were restricted we found a total of 66 articles in different platforms. Duplicated articles were removed leaving 53 articles. The titles and abstracts were subsequently analyzed comprehensively for all of them. Twenty-seven articles were selected for full text review. Three additional articles were found from the references of the selected articles. Finally, 23 articles were selected for final analysis (Flow Diagram Adapted From PRISMA).

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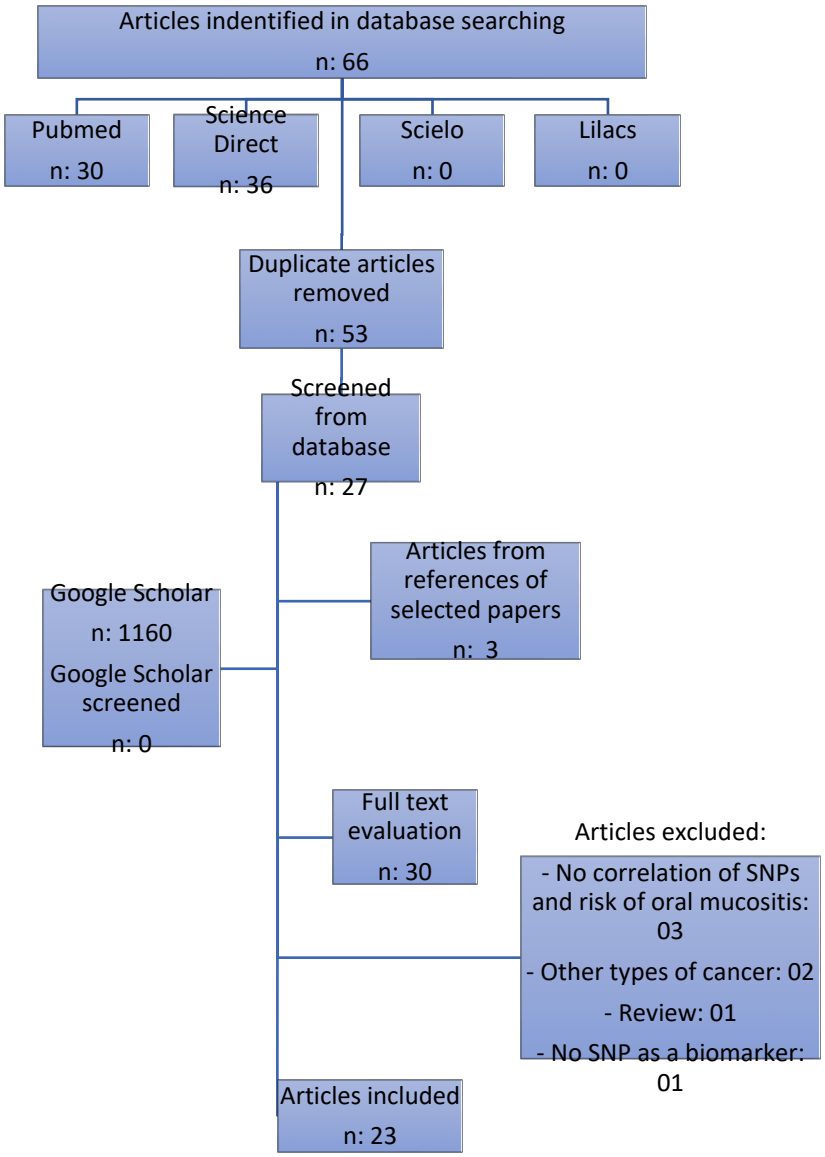

Flow diagram of the studies selections

Study characteristics:

The countries where the studies were conducted were China (10), Poland (04), India (03), Japan (01), Belgium (01), Italy (01), Spain (01), France (01), USA (01).

All articles were published in English, between 2009 and 2021.

The total of individuals from the published articles was 4977. Genome wide association studies contributed with most of the patients. Sample sized ranged from 24 to 1467 patients with HNC. All patients received RT with or without CT. Two articles included surgery as an option.

All articles used genomic DNA extracted from blood samples, except one that used tumor samples stored in liquid nitrogen from diagnostic biopsies.

Table 1 summarizes the main characteristics and findings of the selected articles.

Synthesis of results:

Mucositis SNP associated non-proinflammatory mediator regulated genes Among the 23 included articles, genes from several pathways were analyzed.

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Eight assessed the relationship between acute toxicities and polymorphisms in genes related to DNA damage repair. The most frequently analyzed gene was XRCC1 (Figure 1). One article found no substantial association between SNPs in DNA repair genes and mucositis (Werbrouck et al., 2009).

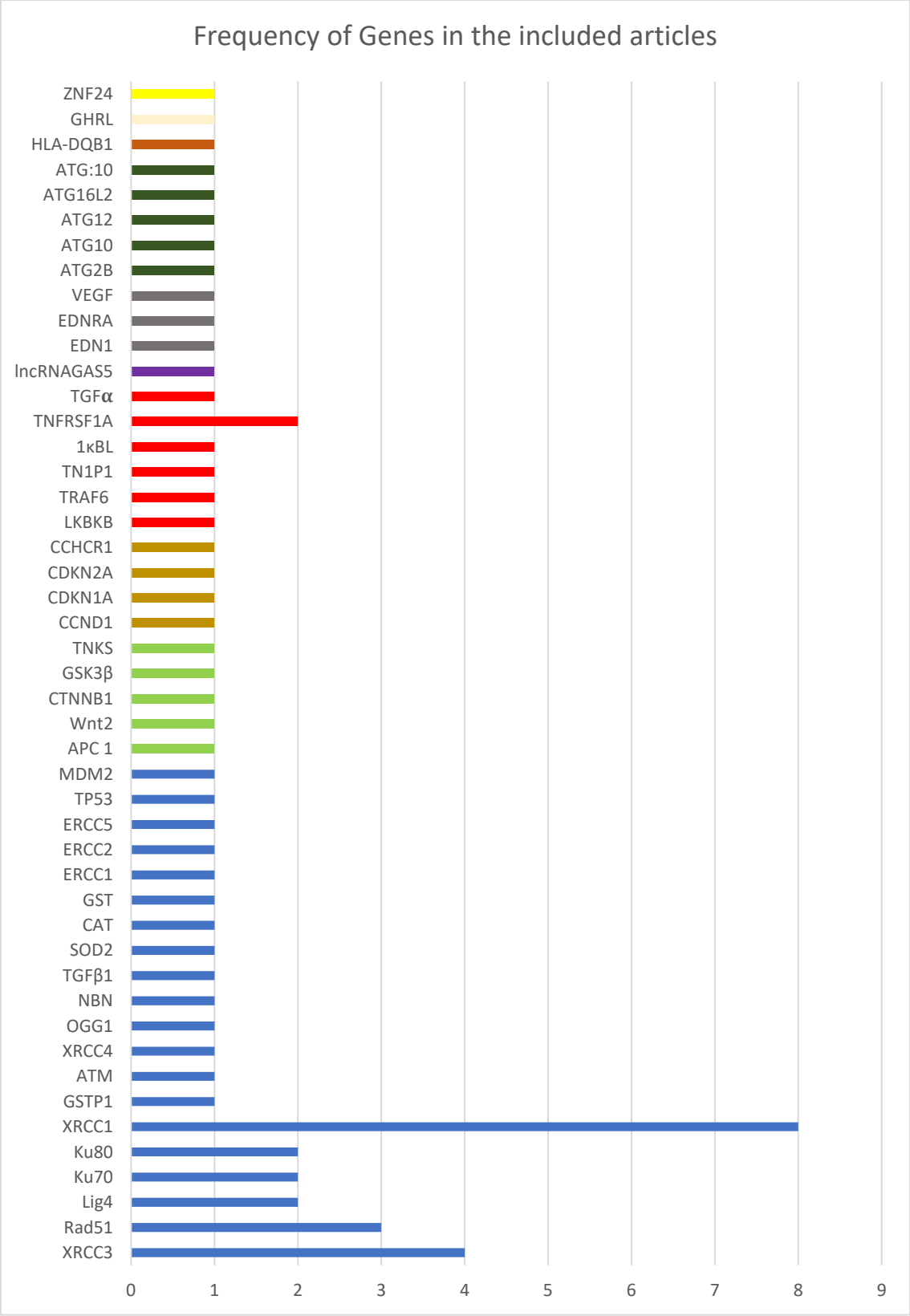

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Figure 1. Frequency of genes in the included articles separated by colors. Blue: DNA Repair genes, Green: Wnt/B Catenin, Brown: Cell Cycle, Red: Inflammatory.

Three groups analyzed and established the relationship between a SNP at codon 399 of the XRCC1 gene (Gupta et al., 2019; Nanda et al., 2018; Raturi et al., 2020). Chen et al. observed no significant difference in the severity of acute OM damage during RT between patients with different genotypes (Chen et al., 2017). However, in one article there was a significant correlation (p 0.011) (Borchiellini et al., 2017) and in another a marginal correlation (p 0.065) (H. Li et al., 2013).

Three articles published results on the relationship between the Arg194Trp polymorphism in the XRCC1 gene and clinical outcomes in patients with head and neck tumors. Li et al. showed the polymorphism was associated with a decreased incidence of grade 3 acute OM compared with the Arg/Arg allele, but with no statistical significance (H. Li et al., 2013). The other two articles concluded that the presence of SNP was significantly related to mucositis, p=0.023 (Nanda et al., 2018) and p=0.01 (Raturi et al., 2020).

Seven SNPs of four genes of the Wnt/β-catenin pathway were investigated. The rs454886 polymorphism of the adenomatous polyposis coli gene was correlated with grade 3-4 OM (p=0.045) (Yu et al., 2016).

Additional studies have found a relationship between mucositis and SNPs in non-coding RNA pathways, in genes encoding ghrelin (Brzozowska, Homa-Mlak, et al., 2018), in the ABCC1 gene pathway (Duran G et al., 2019), and in autophagy-related genes (Z. Yang & Liu, 2019).

Four studies performed a genome-wide association analysis. They were included as they found a link between the occurrence of different polymorphisms and the potential risk of developing mucositis. One study was in the CCHCR1 gene (Q. Li et al., 2021), the others in the TNKSK (D. W. Yang et al., 2020), ZNF24 (Le et al., 2017) and RB1 (Reyes-Gibby et al., 2017) pathways.

Mucositis SNP associated proinflammatory mediator regulated genes

Previous data have established the association of inflammatory cytokines and their pathways in the development, maintenance, and intensity of acute mucositis. Clinical inflammatory conditions are preceded by increased levels of these cytokines. Four articles evaluated the relationship between SNPs in inflammatory cytokine pathways and mucositis.

The cytokine pathways evaluated were TNF, with three articles, and NF-κB, with one article. The TNF receptor, TNFR1, when activated, regulates an apoptotic pathway and may be involved in the development of mucositis. Two articles assessed SNPs in the promoter region of the gene encoding the receptor protein, TNFRSF1A, and showed a significant increase in the likelihood of grade 3 mucositis in the last weeks of RT in CC, TT, or GT genotype carriers (Brzozowska, Powrózek, et al., 2018; Mlak, Powrózek, Brzozowska, Homa-Mlak, Mazurek, Gołębiowski, Korzeb, et al., 2020). The other article addressing the TNF pathway assessed the relationship between the SNP (- 1211 T > C, rs1799964) in the TNF-α gene itself and the occurrence and intensity of OM (Mlak, et al., 2020).

Guo et al. chose 5 SNPs in the NF-κB pathway to relate to the likelihood of acute toxicity. There was no relationship between the polymorphisms and mucositis. However, in the same article, the authors also evaluated SNPs in cyclins, cell cycle regulatory proteins. CCND1 rs9344 was associated with grade 3-4 radiation-induced acute OM (Guo et al., 2017).

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Table 1. Main characteristics and findings of the selected articles.

Author	Country	Year	Primary Sites	Possible Treatments	Number of patients (n)	Dose (Gy)	Signaling Pthway	Sample	Type of study	Main Conclusions	Mucositis as one of the primary end point
Werbrouk et al	Belgium	2009	Head and Neck	RT / RT + CT / Surgery + RT	88	66 - 70	DNA DSB repair genes XRCC3, Rad51, Lig4, Ku70, Ku80	Bood	Cohort	A positive but not statistically significant association was found between the presence of the XRCC3c.562-14 A>G (rs1415120657) polymorphism and the risk of severe acute mucositis (adjusted OR = 1.96; p = 0.178). The presence of one variant allele of Rad51c.-3392 was associated with a small increase in the risk for severe mucositis after RT (adjusted OR = 1.21; p = 0.728). For the Ku70c.-1310 SNP, a negative but not significant association was found with the development of severe acute mucositis.	Yes

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Patresi et al	Italy	2011	Head and Neck	RT / RT + CT	101	54 - 70	XRCC1 c.1196A > G, XRCC3 c.722C > T, RAD51 (c.-3429G > C, c.-3392G > T), and GSTP1 c.313A > G.	Blood	Cohort	The risk of mucositis was significantly increased in patients with XRCC1-399Gln allele genotypes both in chemo-radiotherapy (p = 0.035, HR = 1.72, CI = 1.03–2.86) and in radiotherapy alone (p=0.049, HR=2.50, CI=0.97–6.47) groups.	Yes
Li H et al	China	2013	Nasopharynx	RT / RT + CT	114	66 - 70	XRCC1 (194Arg/Trp and 399Arg/Gln)	Blood	Cohort	XRCC1 399Arg/Gln was associated with higher incidence of grade 3 oral mucosa toxicity, OR = 2.11 (95% CI: 0.951-4.66), p 0.065	Yes
Venkatesh et al	India	2014	Head and Neck	RT + CT	183	60 - 70	ATM, XRCC1, XRCC3, XRCC4, Ku70, Ku80, LIG4, OGG1, NBN, RAD51, TGFb1, SOD2, CAT, GST	Blood	Cohort	There was na association for NBN (rs1805794) polymorphism in univariate and multivariate analysis and severe mucositis	Yes
Yu J et al	China	2016	Nasopharynx	RT / RT + CT	188	66 - 70	7 SNPS Wnt/β-Catenin	Blood	Cohort	The *APC* rs454886 polymorphism was significantly associated with acute grade 3–4 radiation-induced oral mucositis in additive (p 0.045) and recessive models (p 0.038) after	Yes

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										adjustment for BMI. Individuals carrying the minor A allele of the rs454886 polymorphism had an increased risk of acute grade 3–4 radiation-induced oral mucositis.	
Guo Z et al	China	2017	Nasopharynx	RT + CT	505	68 - 72	lncRNA *GAS5*	Blood	Cohort	Slight relationship was found in the discovery stage for severe oral mucotisis and rs2067079, as well as rs6790 (P=0.049). Neither of the two SNPs were verified in the validation stage, nor in the combined cohort. Patients of rs2067079 TT genotype receiving DP for IC regimen (TT vs CC, OR=3.031, P=0.047) or CCRT regimen (TT vs CC, OR=21.882, P=0.043) were subjected to high risk of oral mucotisis.	Yes
Chen H et al	China	2017	Nasopharynx	RT / RT + CT	114	70 - 76	Base repair XRCC1 Codon 399 SNP	Blood	Cohort	In locally advanced nasopharynx cancer patients with different genotypes, the injury degree of acute radiation oral mucositis showed no significant difference (P = .449, 95% CI: 0.691–2.304)	Yes

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Guo C et al	China	2017	Nasopharynx	RT / RT + CT	154	66 - 70	3 SNPS Cell cycle / 5 SNPS NF-κB	Blood	Cohort	In stratification analysis, CCND1 rs9344 was related with grade 3–4 acute radiation-induced oral mucositis in recessive model among patients < 51 years old	Yes
Le Z et al	China	2017	Nasopharynx	RT / RT + CT	24	66 - 70.4	Genome Wide Screening	Blood	Cohort	The SNP rs11081899-A in ZN24 was significantly associated with an enhanced risk of severe mucositis (OR = 14.631, 95% CI = 2.61-105.46, p = 1.2 × 10−4)	
Ma W et al	China	2017	Nasopharynx	RT / RT + CT	180	66 - 77	Angiogenesis related genes 3 SNPS EDN1 / 3 SNPS EDNRA / 2 SNPS VEGF	Blood	Cohort	GT genotype in EDN1 rs1800541 was significantly associated with an elevated risk of developing grade 3+ oral mucositis (p=0.038)	Yes
Reyes-Gibbi C	USA	2017	Head and Neck	RT / RT + CT / Cirurgia + RT	NI	NI	Informative gene network analysis	x	x	SNP in *RB1* (rs2227311, *p*-value = 0.034, OR = 0.67) showed a protective effect for oral mucositis	Yes
Borchiellini et al	France	2017	Head and Neck	RT / RT + CT	122	60 - 70	ERCC1 / ERCC2 / XRCC1 / M2M	Diagnostic biopsy	Cohort	The presence of the G allele of MDM2 309 (genotypes TG or GG) or the Thr allele of ERCC1 251 (genotypes Lys/Thr and Thr/Thr) was associated with a higher risk of acute and/or early G3-4 DMEX.	No

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Nanda S et al	India	2018	Oral cavity, pharynx, larynx	RT + CT	101	66 - 70	Base repair XRCC1 Arg194Trp	Blood	Cohort	Patients with polymorphic variant had higher grade > 2 oral mucositis 35.8% vs. 16.0% (OR: 2.91; 95% CI 1.13-7.46; p=0.023)	Yes
Brzozowska et al.	Poland	2018	Head and Neck	RT / RT + CT / Cirurgia + RT	65	60 - 70	GHRL	Blood	Cohort	AA genotype was associated with 7-fold decrease in the risk of occurrence of intensified oral mucositis (grades 2 and 3 according to RTOG) in the sixth week of RT	Yes
Brzozowska et al.	Poland	2018	Head and Neck	RT / RT + CT	58	66 - 70	TNFRSF1A	Blood	Cohort	Patients with TT or GT genotype demonstrated higher risk of manifestation of grade 3 mucositis toxicity in 5th week of RTH (p = 0.041; OR = 9.240; 95% CI: 1.101–77.581) compared to GG carriers in whose grade 1 and 2 of mucositis reactions was observed more frequently.	Yes
Duran G et al	Spain	2019	Oral cavity, pharynx, larynx, unknown primary	RT + CT	110	50 - 76	ABCC1	Blood	Cohort	For rs1045642, patients with the variant T/T genotype showed higher acute mucositis than C/C or C/T genotype patients (47.1% vs 24.1%; OR: 3.42; 95% CI: 1.04-11.21; P = .042 in a recessive model).	Yes

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Yang Z et al.	China	2019	Nasopharynx	RT / RT + CT	468	66 - 70	Autofagia genes (ATG)	Blood	Cohort	*ATG10* rs10514231 and *ATG16L2* rs10898880 were significantly associated with the occurrence of grade 3–4 oral mucositis	Yes
Gupta A et al.	India	2019	Oropharynx	RT / RT + CT	179	66	XRCC1 / XRCC3 / XRCC4 / XRCC6 / ERCC4 / Lig4 / ATM	Blood	Cohort	Homozygous AA genotype of XRCC1 (rs25487) and certain clinical characteristics are likely to develop severe acute mucositis (p 0.024)	Yes
Mlak R et al.	Poland	2020	Head and Neck	RT / RT + CT	60	54 - 70	(_135 T>C, rs767455) of TNFRSF1 A	Blood	Cohort	SNP (_135 T>C) of the TNFRSF1 A gene may act as a predictor of OM occurrence in patients with HNC treated with IMRT	Yes
Mlak R et al.	Poland	2020	Head and Neck	RT / RT + CT	62	66 - 70	TNFα rs1799964 (-1211 T > C)	Blood	Cohort	The presence of CC genotype was related with over sevenfold (OR = 7.33, 95% CI 1.120– 44.96, p = 0.031) and 23-fold (OR = 23.15, 95% CI 1.24– 432.14, p = 0.035) higher risk of 3rd degree OM development after the 5th and 7th week of RTH, respectively.	Yes
Yang D et al.	China	2020	Nasopharynx	RT / RT + CT	1467	68 - 76	Genome-Wide Association Study	Blood	Cohort	The SNP rs117157809 located in TNKS gene was associated with increased risk of oral mucositis (95% CI 2.10–6.57; P = 6.33 × 10−6).	yes

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Raturi V et al.	Japan	2020	Larynx	RT + CT	134	70	XRCC1 Arg194Trp	Blood	Cohort	XRCC-1 Arg194Trp polymorphism is significantly associated with oral mucositis (P- .01).	Yes
Quinghua L et al.	China	2021	Head and Neck	RT / RT + CT	500	NI	Genome-Wide Association Study	Blood	Cohort	Both SNP rs1265081 in CCHCR1 gene (allele A vs C: OR=1.41, 95% CIs=1.08–1.86, P=0.012) and rs3135001 (allele T vs allele C: OR=0.53, 95% CIs=0.35–0.79, P=0.002) were significantly associated with the occurrence of grade 3–4 oral mucositis.	

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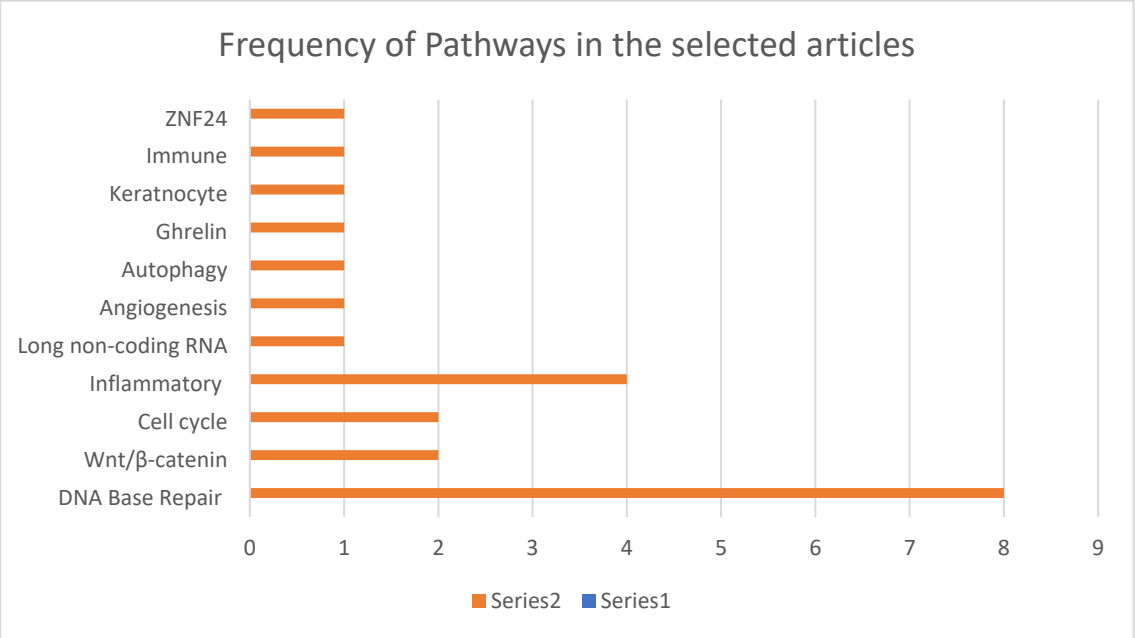

Figure 2. Frequency of different pathways in the included articles.

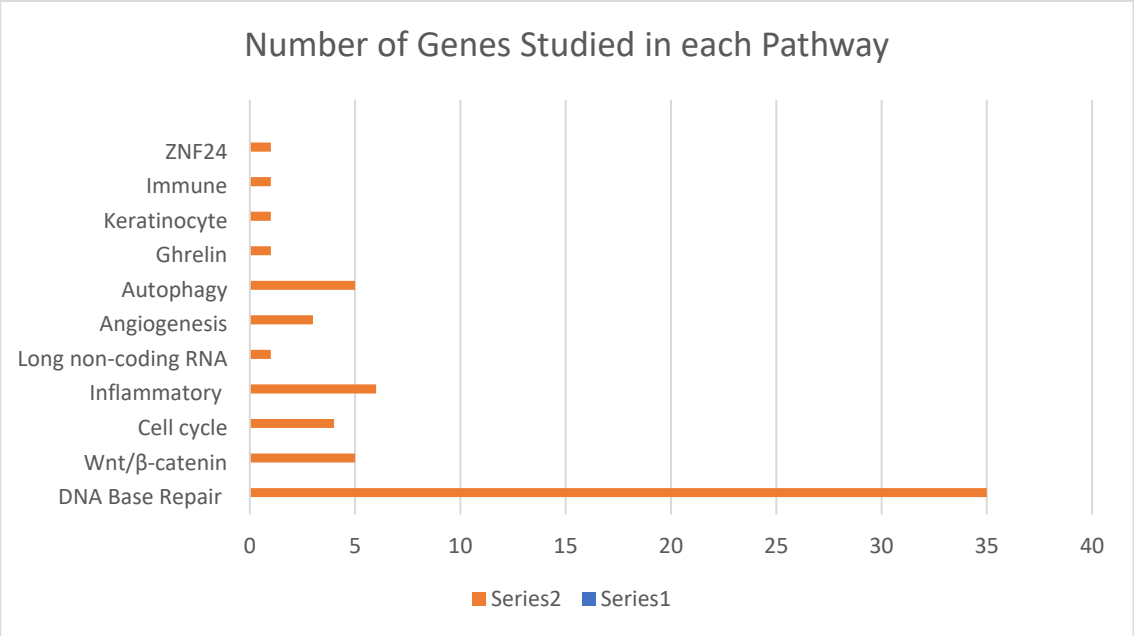

Figure 3. Number of genes studied in each pathway.

Study Risk of Bias and Quality Assessment

All the references were individually assessed using the NOS tool, with a maximum score of nine. Nine articles (39.1 %) obtained a score of six, 11 (47.8 %) a score of five. Three (13 %) articles scored four, and only these were considered to be of fair quality (Figure 4).

DISCUSSION

In recent years much progress has been made in understanding the molecular pathways associated with the pathophysiology of diseases, as well as treatments and their adverse effects. In oncology it is no different and several signaling pathways have been described and the personalization of the diagnostic and therapeutic approach is a remarkable advance. The treatment

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of HNC based on RT combined with CT represents the possibility of curing certain diseases that previously could not have curative surgical approaches, in addition to offering a chance of organ preservation in an anatomical region very sensitive to these changes. One of the most common and debilitating toxicities, with the potential to compromise therapeutic outcomes related to this strategy, is mucositis.

Mucositis is a common and often debilitating side effect of cancer treatment that involves damage to the mucous membranes lining the gastrointestinal tract, particularly in the oral and oropharyngeal regions. It can be caused by CT, radiation therapy, or a combination of both, and can lead to a range of clinical and symptomatic manifestations, including erythema, ulceration, pain, and difficulty eating and drinking (Peterson DE, 2012). Mucositis can also increase the risk of infection and other complications (Cinausero et al., 2017)

Historically mucositis was seen as a result of a direct action of RT or CT on the cells of the basal epithelial layer. However, this simpler picture could not explain the complex interactions that started to be described in the submucosal layer. The concept that mucosal injury is a biological and multifactorial process is relatively new.

In 2004, Sonis et al. published a study describing the aspects of mucositis development as a dynamic process divided into phases, initially involving the generation of free radicals by direct action of RT and/or CT (Sonis, 2004). Local damage triggers an inflammatory response, activating several biological pathways, including nuclear factor kappa-B (NF-kB). This transcription factor, which can also be directly activated by RT and/or CT, induces gene expression of pro-inflammatory cytokines such as interleukin-6 (IL-6), interleukin-1β (IL-1β), and tumor necrosis factor α (TNF-α), which are apparently increased in mucositis. TNF-α may engage in a positive feedback mechanism with NF-kB, increasing its concentration, eventually producing a massive release of cytokines (pro-inflammatory cytokine storm), amplifying the process. The clinical condition then develops with the onset of disease-related signs and symptoms, such as ulcers. At this point, the patient is more susceptible to infections, which can prolong mucositis as the activation of macrophages can release more inflammatory cytokines.

Recent advances in molecular and cell biology have provided targets for mechanism-based interventions to prevent and treat mucositis. Normando et al. evaluated several biomarkers for their association with the development of OM, including epidermal growth factor, C-reactive protein, genetic polymorphisms, tumor necrosis factor alpha (TNF-α), erythrocyte sedimentation rate, growth factors, acute phase inflammatory markers, cytokines, general proteins, plasma antioxidants, apoptotic proteins, and cells. The meta-analysis showed an expression of polymorphisms in XRCC1, XRCC3 and RAD51 genes, as well as an expression of protein biomarkers, in patients with an increased risk of developing OM. However, the effectiveness of these biomarkers in predicting mucositis risk and guiding treatment decisions is still under investigation (Normando et al., 2017)

Genetic polymorphisms can influence gene expression by affecting various regulatory elements within the genome. Among genetic polymorphisms, SNPs are the most common type of genetic variation in the human genome. Recently, several studies have explored the relationship between SNPs and susceptibility to mucositis in cancer patients. In this systematic review, we analyzed the non-pro-inflammatory and pro-inflammatory genes regulated by SNPs in HNC patients undergoing RT and CT.

Pro-inflammatory cytokines play a decisive role in the development of mucositis. The apoptosis process regulated by TNF occurs via the TNFR1 receptor. Genetic alterations such as SNPs in the gene that codes for the receptor can alter its expression and function. Brzozowska et al. showed that the presence of the T allele in the TNFRSF1A gene is associated with an increased risk of manifestation of grade 3 OM in patients with HNC undergoing RT. The study found that patients with TT or GT genotype demonstrated a higher risk of grade 3 OM manifestation at week five of RTH compared to GG carriers. The results indicate an association between the TNFRSF1A gene SNP (rs4149570) and the risk of more severe RT-related OM in patients with HNC .

In their work, Mlak et al. (2020) showed that the CC genotype of the TNFRSF1 A gene is associated with a more severe course of OM. The SNP identified in this study is located in the

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regulatory region of the TNFRSF1 A gene. Specifically, it is the SNP (rs767455) that has been found to be involved in the regulation of TNFR1 protein expression and may potentially modulate the risk of OM in HNC patients treated with RT, and is an independent prognostic factor of poor overall survival in HNC patients undergoing intensity-modulated radiation therapy. The TT genotype, in contrast, had an inverse protective effect. However, due to the limitations of the study, further research is needed to confirm these results.

Figure 2 shows that two SNPs (rs4149570 and rs767455) located in the TNFRSF1A gene are associated with more severe OM.

Another inflammatory pathway studied was the NFKB transcription factor, which when activated causes up-regulation of genes that result in increased cytokine production. The κB kinase inhibitor gene IKBKB rs12676482 was related to grade 3-4 radiation-induced acute myelosuppression, but not to mucositis (Guo et al., 2017).

In the studies that have evaluated SNPs in non-inflammatory pathways, the most investigated have been alterations in DNA damage repair genes. DNA damage repair is a mechanism which is related to radiosensitivity in both tumor response and treatment-related adverse effects. Normal tissues depend on this mechanism to recover between RT sessions from damage caused by RT and alterations in this mechanism can exacerbate toxicities, increasing variability between individuals receiving the same treatment. The included articles evaluated polymorphisms in candidate genes previously related to radiosensitivity. The most common gene studied was XRCC1, which is associated with the ability to detect and repair three of the most common DNA errors: single-strand breaks, double-strand breaks, which have greater biological significance, and base excision repair. The most frequently searched SNP was c1196A>G p.Gln399Arg.

The risk of bias and the quality of the articles were assessed using the NOS tool, which establishes points for pre-established criteria. The articles generally have a similar design, reducing the possibility of bias. In general, the articles were considered to be of good quality and to have a low risk of bias, since most of them scored five or more. In all the publications, the control groups were not patients who had not been exposed to the treatment, but patients with milder toxicities, which is a characteristic of the study design. However, according to the NOS scale, it is not possible to score them in this respect. Another issue that is not specified in most references is the demonstration that the main outcome, mucositis, is not present at the start of the studies. It is understood that mucositis was not present before the start of RT, but when this is not specified, it cannot be scored using the scale.

This systematic review demonstrates that SNPs in different biological pathways have the potential to be biomarkers and to function as predictors of patients who will develop severe mucositis. The most studied biological pathway was that involving DNA damage repair genes. However, considering the involvement of cytokines and inflammatory pathways in the pathophysiology of mucositis, we believe that this is a promising area in the study of the predilection of this condition. As studies collect more robust data on biomarkers in different pathways, we will be closer to developing a more personalized treatment strategy for a clinical condition that is costly for healthcare systems and so debilitating for patients who already have a very challenging type of cancer.

Supplementary Materials: The following supporting information can be downloaded at the website of this paper posted on Preprints.org.

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