Gene Polymorphism in Genomic Stability Pathway: A Genetic Driver behind the Emergence of Head and Neck Cancer

Garima Avasthi [1], Amresh Gupta[1], Tridiv Katiyar [2], Vinay Yadav [2], Devendra Parmar [2] Pawan Kadwe [3], Sudhir Singh [4], Madhup Rastogi [5]

[1]*Associate Professor, Goel Institute of Pharmacy and Sciences, Faizabad Road, Lucknow, U.P., India.*

[2]*Research Associate, System Toxicology & Health Risk Assessment Group, CSIR-Indian Institute of Toxicology Research (CSIR-IITR), Vishvigyan Bhawan, Mahatma Gandhi Marg, Lucknow, Uttar Pradesh, India.*

[3]*Research Scholar, Department of Biotechnology, Chhindwar University, Chhindwara, Madhya Pradesh, India.*

[4] *Associate Professor, Department of Radiotherapy, King George's Medical University, Chowk, Lucknow, U.P., India.*

[5]*Professor, Department of Radiation Oncology, Dr. Ram ManoharLohia Institute of Medical Sciences, Gomti Nagar, Lucknow, U.P., India.*

Corresponding Author: garimaniec@gmail.com

Abstract: - Head and Neck cancer is a devastating and unresectable disease, is the sixth most prevalent cancer accounting for 3% of all cancer. Majority of head and neck cancer originated from mucosal lining of the upper aero-digestive tract part especially in larynx, pharynx, oral cavity and nasal cavity collectively termed head and neck squamous cell carcinoma. Tobacco and alcohol are crucial risk factors of head and neck cancer. Additional etiologies that cause head and neck cancer are viral infection and genetic susceptibility factors and its association with head and neck cancer is still to be understood. Genetic instability is one of the prevalent features of all types of cancers. Genetic blueprint (DNA) is usually damaged by exogenous, endogenous mutant agents and genetic variant in combination with environmental exposure to exogenous/endogenous carcinogens is the main factor responsible for differences between individuals. Single nucleotide polymorphisms in DDR (DNA damage repair) genes are accountable for multiple cancers including head and neck cancer. In this time line article, we focus on the correlation between polymorphisms in the genomic stability pathway and emergence of head and neck cancer. Additionally, we also highlight the various treatments implicated in head and neck cancer.

Key Words: ***—DNA Repair, DNA Damage, Single Nucleotide Polymorphisms (SNPs), Genetic Susceptibility, and Head and Neck Cancer.***

I. INTRODUCTION

Head and Neck cancer (HNC) consists of a heterogeneous group of tumors with multiple cellular origins and located at multiple anatomical sites within the head and neck regions. Most of the head and neck cancers are HNSCC (head and neck squamous cell carcinoma). It is classified as the sixth most prevalent cancer while the 7th most leading cause of cancer is associated death globally with 650,000 new cases appearing/year [1, 2, 3].

Manuscript revised April 27, 2022; accepted April 28, 2022.
Date of publication April 30, 2022.

This paper available online at www.ijprse.com

ISSN (Online): 2582-7898; SJIF: 5.59

HNC includes the neoplasm of the larynx, pharynx, oral cavity and nasal cavity. Appearance of a lump or nodule in the lymph region is an early symptom of HNC [4, 5]. The most prominent features of HNSCC are a lump in the neck, sore throat, cough, difficulty in swallowing food, bleeding from mouth and difficulty in breathing and speaking [6]. Global burden of HNSCC is firmly linked with specific lifestyle (excessive consumption of alcohol and tobacco) and environmental factors (UV light, virus-human papillomavirus and Epstein-Barr virus) or both [7, 8]. Several epidemiological studies showed that consumption of alcohol and tobacco are the crucial risk factors of HNC [9, 10] and may have synergistic effects. Family history associated with cancer is another crucial risk factor for the development of HNC suggesting that genetic factors may promote the susceptibility of HNC [11]. HNC accounts for 3% of all

malignancies in the United States with 66,000 new cases while 14,600 deaths per year [12]. Males are more prone to HNC in contrast to females with a ratio of 4:1 especially in South Central Asia which accounts for 25% of all cancers [13]. The frequency of occurrence of HNC varies across the population of countries [14]. Occurrence of oropharynx cancer in male is more frequent in France while in case of females, it is more frequent in India [15]. Highest incidence rate of oro-pharyngeal carcinoma has been reported in India with 68.6% of patients with advanced stage [16]. Genome of human is persistently exposed to endogenous (methylating agent, aldehydes, hydrolytic deamination, reactive oxygen species and carbonyl stress) and exogenous agents (UV light, ionizing radiation, toxin, pollutant and chemical) [17, 18]. These mutational agents may trigger an abnormal DDR response resulting in apoptosis, chromosomal instability and uncontrolled proliferation of cells [19, 20, 21]. DDR genes play a pivotal role in protecting the cells from DNA insult and in maintaining the integrity of humans. Additionally, replication of the insulted DNA triggers mutation that leads to disease. Hence, any alteration in DDR genes could enhance the risk of HNC [22]. Multiple DDR pathways are available to maintain the integrity of human genome including nucleotide excision repair (NER), base excision repair (BER), mismatch repair (MMR), direct reversion repair (DRR) and double-strand break repair (DSBR) [23]. In this overview, we focus on the correlation between polymorphisms in the genomic stability pathway and emergence of head and neck cancer.

1.1 Genetic Susceptibility - Head and Neck Cancer

Only some of the cases of alcohol and tobacco users develop HNSCC which proposed that genetic factors may have a role in the development of HNSCC. A meta-analysis conducted by Foulkes et al., [24] reported that the risk of HNSCC is found to increase in first-degree relatives of patients with HNSCC. There are two important genetic factors that may increase the susceptibility of individuals to HNSCC i. e. carcinogen metabolizing and DNA repair enzymes. Carcinogen metabolizing enzymes are important players as they maintain the balance between detoxification of potential and metabolic activation of carcinogens. Hence, polymorphisms in genes of carcinogen-metabolizing enzymes may increase the susceptibility of individuals to HNSCC. Exposure to environmental carcinogens impaired the DNA by the way of alkylation, oxidative stress, and formation of adducts, and single or double strand breaks. Genetic differences among individuals particularly in DNA repair [25, 26, 27 28] and metabolic enzymes [29, 30, 31] will affect the risk of cancer. Risk of HNSCC may increase in the individual having altered capacity of the DNA repair mechanism. NER (nucleotide excision repair) pathway plays a key role to remove the oxidative DNA damage and bulky mono-adduct [25]. Burgeoning evidence reported the relationship between abnormalities in the DNA repair and HNSCC [32, 33, 34]. Gene products of XRCC1 interact with poly (ADP-ribose) polymerase, polymerase-β and DNA ligase-III to participate in the BER (base excision repair pathway). XPD (xeroderma pigmentosum group-D) possesses activities of DNA helicase and single-stranded DNA-dependent ATPase that are involved in unwinding the region of damaged DNA. One of the previous studies reported the five polymorphisms in a single base of NER genes, two polymorphic sites in XPD/ERCC2 [35]. A study led by Shen et al., [36] reported additional 13 polymorphisms associated with XPD, four in XRCC3 and three in XRCC1. Accumulating evidence demonstrated the association between polymorphism in XRCC1 and XPD with risk of head and neck cancer [37, 38, 39].

1.2 DNA Repair genes - Head and Neck Cancer

Constant degradation of genomic material occurs due to exposure of exogenous and endogenous factors. Genomic instability is the important manifestation of cancer which is caused by alternation in the DNA repair pathway. There are many different kinds of DNA damage or lesions which are dealt with different pathways including BER, NER, MMR (mismatch repair), single stranded break and double stranded break. Basically, single stranded break is considered as an integrated part of BER, NER and double stranded break pathway. Most severe condition associated with DNA damage is double stranded break [40]. NER and BER involve single stranded break which may transform into double strand break if irreparable during the replication process [41]. Non-homologous end joining (NHEJ) and homologous recombination (HR) are two pathways which are involved in repairing double strand break [41]. Most commonly SNPs associated with genomic stability pathways are represented in **Table-1**.

1.3 Base excision repair (BER) pathway

It plays a key role to protect the genetic material from the deleterious effects of reactive oxygen species (ROS). In spite of this, it also repaired the single stranded break [42].

Inherited mutation in genes associated with the BER pathway is very uncommon. However, polymorphism in some genes (OGG1, APE1 and XRCC1) has been found to genetically link with risk of HNSCC [43]. OGG1 removes the glycosidic bond between sugar moiety and altered base leaving behind apurinic site (AP) which is incised and the resultant gap is repaired by a phosphodiesterase followed by DNA ligase [44]. More than 439 SNP has been reported for OGG1 and S326C is the most commonly studied SNP (rs1052133) which is located in exon 7 of human (h) OGG1. A few studies reported the association of S326C SNP with the development of head and neck cancer [44, 46, 47, 48]. A case control study led by Elahi et al., [49] reported the association of S326C SNP with head and neck cancer. One of the earlier studies demonstrated that S326C SNP may enhance the risk of HNSCC in case of smoking [47]. The results associated with S326C SNP are still contradictory as few studies reported the negative results which may be due to genetic differences among ethnic groups, small sample size and exposure of carcinogen in different populations. APE1, an enzyme that catalyzes the hydrolysis of phosphodiester bonds at the 5` site of AP site. It also repairs the single strand breaks which are generated either through the enzymatic removal of base or ROS [50, 51]. Eighteen of 123 SNP of APE1 are very frequent and the most highly studied SNPs are T656G (rs1760944) and D148E (rs3136820). Earlier studies showed that T656G SNP alter the transcriptional activity of APE1 while D148E delays the meiotic activity in the cells post ionizing exposure and eventually contributes to development of cancers [52, 53, 54]. A hospital care case control study conducted by Li et al., [55] found that no association between the alteration in APE1 and risk of HNSCC. A study conducted by Matullo et al., [56] found that D148E SNP was associated with decreased incidence of head and neck cancer. A meta-analysis conducted by Gu et al., [57] found that D148E SNP acts as a low penetrance risk factor for head and neck cancer. XRCC1, another BER protein which recognizes the single strand break and more than 200 SNP have been reported with most extensively studied SNPs are R194W (rs1799782), R280H (rs25489), and R399Q (rs25487). Several previous studies demonstrated that R399Q SNP was linked with different kinds of cancers [58, 59, 60]. Hu et al., [61] reported that R194W SNP was found to link with a risk of development of cancer while the R280H SNP was linked with an enhanced risk of cancer. Li et al., [55] reported that R399Q was found to significantly link with risk of head and neck cancer in Asian population. A recent meta-analysis conducted by Xia et al., [62] found that the R399Q was associated with the development of head and neck cancer among Caucasian. A few studies reported that the R280H decreases the genomic stability and modulates the sensitivity to ionizing radiations [54, 63]. Dutta et al.,[64] found that the R399Q was found to link with inferior survival functions. Applebaum et al., [65] reported that the polymorphism in XRCC1 confirms the susceptibility of development of HNSCC with respect to smoking.

1.4 Nucleotide Excision Repair (NER) Pathway

NER pathway plays a key role to maintain the integrity of genomic material particularly repairing the multiple bulky helix distorting DNA modifications [66]. Tumors with up-regulated NER possess an intrinsic resistance to chemotherapy and radiotherapy [67] resulting in continued tumor growth and metastasis even post treatment [68]. Most extensively studied genes of the NER pathway that were associated with the development of head and neck cancer are XPA, XPC, ERCC1, ERCC2/XPD, ERCC4/XPF and ERCC5/XPG. XPA involves DNA excision repair and transcription associated repair pathway [69]. Several lines of evidence reported that Polymorphism in XPA was associated with progression of HNSCC [70, 71]. The most commonly investigated SNP of XPA was A23G located in 5` UTR (un-translated region). The patients with XPA polymorphism, especially A23G, had a decreased risk of lung cancer in Korean [72] and Caucasian populations [73]. Several lines of evidence reported the association between risk of head and neck cancer and A23G SNP [74, 75, 76, 77]. A study performed by Sugimura et al., [74] found that the A23G SNP was linked with risk of oral squamous cell carcinoma. Bau et al., [77] also reported similar findings with A23G SNP. A meta-analysis based on case control studies found that the A23G SNP was associated with the developmental risk of head and cancer [78]. XPC is another candidate of NER pathway which involves in recognition of DNA damage and changing the conformation around the lesion [79]. Three most common SNP (poly-AT insertion +/- deletion, A499V and K939Q) have been identified. A small case control study carried out by Shen et al., [80] found that the risk of HNSCC was found to be associated with the XPC-PAT + allele. However, a large case-control study conducted by An et al., [81] reported that only A499V SNP was correlated with enhanced risk of HNSCC. One of the earlier studies reported that expression of XPC may influence the risk of HNSCC. They also reported that there was no association between

XPC-PAT and HNSCC risk in a Korean population [82]. A recent study showed that patients with homozygous alleles for the XPC (A>C) develop HNSCC risk in the early stage in North Indian Population [83]. ERCC1 is a critical protein in the NER pathway and polymorphism of XRCC1 has been identified to enhance the susceptibility of carcinogenesis [84]. Three common ERCC1 SNPs are Asn118Asn (rs11615), IVS5 + 8092>A (rs321986), and 33C>A (rs3212961) which was most extensively studies among 437 SNPs. A few meta-analyses reported that only IVS5 +33C>A and Asn118Asn SNPs are low penetrance risk factors for the development of cancer [85, 86]. Most of the studies were focused on 8092C>A SNP and risk of head and neck cancer [74, 76, 81, 87]. A small case control study reported the link between 8092C>A SNP of ERCC1 and mRNA expression and they observed the lower expression of ERCC1 mRNA in HNSCC patients in contrast to controls [88]. One of the previous studies reported that the combination of 8092C>A SNP with the XPDAsp312Asn SNP may enhance the HNSCC risk [89]. However, the results with 8092 C>A SNP are still contradictory as few studies have not observed an association between HNSCC risk and 8092 C>A in different genetic models [81, 85]. A recent study suggested that the 8092C>A SNP was correlated with increased risk of oral squamous cell carcinoma [90]. XPD is another enzyme of the NER pathway which removes UV induced DNA lesions, chemically induced bulky adducts and DNA cross links. Asp312Asn (rs1799793) and Lys751Gln (rs13181) are two well studied SNP among 560 SNPs. A study led by Hou et al., [91] reported that The Asn312 variant allele of XPD was correlated with decreased repair of DNA adducts. The K751Q SNP has also been found to be associated with decreased DNA repair proficiency [92]. Sturgis et al., [89] firstly reported the link between risk of HNSCC and the Asp312Asn SNP. They also observed that this SNP in combination with ERCC1 8092C>A SNP had a significant correlation with risk of head and neck cancer. One of the studies reported the elevated risk of head and neck cancer with K751Q SNP of XPD which was more prominent in Europeans in contrast to Asians [93]. XPF is also known as ERCC4 which possess catalytic domain of DNA nuclease [94] and involve in excising bulky DNA adducts. Only two common SNPs Ser835Ser (rs1799801) and Arg415Gln (rs1800067) have been extensively investigated [76, 81, 95]. A meta-analysis reported that two SNPs were not found to correlate with the risk of head and neck cancer [96]. Inconsistent results are associated with XPF polymorphism and HNSCC risk. ERCC5 also termed as XPG possesses endonuclease activity which is important for two step incision in NER [97]. Only the 1104 N> H SNP (rs17655) has been well studied and correlated with susceptibility of head and neck cancer risk. Although, this SNP together with SNPs of multiple other genes of NER pathway may contribute to alter the DNA repair capacity phenotype while none of the studies observed statistically significant correlation with head and neck cancer risk [76, 98, 99]. However, a recent meta-analysis conducted by Hu et al., [100] reported a positive correlation between XPG polymorphism and increased susceptibility of head and neck cancer.

1.5 Mismatch Repair (MMR) Pathway

MLH1 and MSH2 are chief proteins of the MMR pathway that recognize and correct the replication errors. Numerous SNPs of identified in MLH1 and MSH2 have been reported while few of them was extensively investigated for their correlation with risk of cancer like the 93G>A SNP (rs1800734) of MLH1 which is reside in the promoter region [85]. Most of the research focused on the association 93G>A SNP with risk of colorectal cancer. Decreased expression of MSH2 has been observed in HNPCC (hereditary non-polyposis colon cancer) as well as in other human cancers. The Gly322Asp SNP of MSH2 gene which is located in the coding region and associated with modest reduction in MMR efficiency. Although, none of the studies have reported the association of both the Gly322Asp and 93G>A SNPs with head and neck cancer risk. There are two MMR proteins (PMS2 and MSH6) which interacts with MLH1 and MSH2 respectively and they reported that the alteration in MSH6 expression can disrupt the integrity of MMR while PMS2 plays a key role in repairing DNA damage by forming a complex with MLH1 and MSH2 which bounds with mismatched bases. Numerous SNPs have been reported for MSH6 (1013) and PMS2 (945) while inherited mutations were the most extensively investigated studied with risk of colorectal cancer. A study led by Nicolaides reported the association of PMS2 SNP with HNPCC cancer. Inherited mutations in MSH2 and MLH1 are more frequently observed in colorectal tumors or HNPCC because these tumors possess microsatellites (a marker for malfunction of MMR) that were not frequent in head and cancer.[87]

1.6 Direct reversion Repair (DRR) Pathway

MGMT (O6-methylguanine DNA methyltransferase) is enzyme of the DRR pathway which transfers the -CH3 group from the O6-position in guanine and onto the cysteine residue

present in the enzyme. One of the studies reported an increased incidence of nitrosamine-induced tumorigenesis in MGMT knockout mice. Two common SNPs (L84F and I143V) associated with MGMT have been extensively studied for their roles in the development of head and neck cancer. Zhang et al., [91] reported that none of the SNPs of MGMT was associated with HNSCC risk but the combined effect of multiple MGMT allelic variants may promote the risk of HNSCC. Several studies demonstrated that the Leu84Phe SNP was not correlated with HNSCC risk. [79]. A meta-analysis done by Cai et al., [95] showed that aberrant methylation of the MGMT promoter was significantly associated with HNSCC risk. A recent study showed that hypermethylation of MGMT is a critical event in head and neck cancer [85].

1.7 Double Strand Break Repair (DSBR) Pathway

Double strand break is the most severe kind of DNA damage which is basically repaired by homologous recombination and non-homologous end joining pathway [70].

1.7.1 Homologous Recombination (HR):

HR occurs during meiotic division in which similar DNA sequenced from the chromosome of parents. Polymorphism in some of the genes (XRCC2, XRCC3, RAD51 and NBS1) of HR was studied for their roles in the development of HNSCC risk. XRCC2 (X-ray repair cross-complementing 2) is located on the long arm of chromosome 7 (7q36.1) which is a critical member of the HR pathway and it is involved in the progression of various cancers including head and neck cancer. R188H (rs3218536) SNP of XRCC2 is the most common SNP among 661 SNPs has been identified in epidemiological investigations. One of the earlier studies reported the association between R188H SNP and risk of UADT (upper aero-digestive tract) cancer [12]. In spite of this, R188H was found to be associated with an enhanced risk of oral cancer [61]. On the contrary, the R188H and other three SNPs associated with the promoter region have been correlated with decreased risk in other kinds of cancers like bladder cancer [72]. One of the studies reported that the combined effect of tobacco and polymorphism in XRCC2 gene enhanced the risk of head and neck cancer. Saeed et al., [24] studied that polymorphism in XRCC2 gene is directly related with enhanced risk of head and neck cancer. XRCC3 is a member of the RAD51 family and participates in the HR of double strand DNA break and cross-links [25]. Reduced HR has been reported in XRCC3 deficient cell lines [94]. The Thr241Met (rs861539) SNP in XRCC3 among 438 SNPs was most commonly investigated which has been found to have marginal effect on DNA repair capacity. A meta-analysis conducted by Yin et al., [27] found an association between the T241M SNP and risk of head and neck cancer. One of the studies showed that polymorphism in XRCC3 may affect the survival and risk of HNSCC [58]. A recent study reported an association between the C722T SNP and enhanced HNSCC risk [69]. RAD51 is involved in HR to maintain the stability of chromosomes by repairing the double strand break and DNA cross-links [90]. It is associated with the products of BRCA1 and BRCA2 (tumor suppressor gene) suggesting that any alteration in recombination may culminate with tumor development [31]. Kayani et al., [32] showed that polymorphism in RAD51 may act as a biomarker for the susceptibility of head and neck cancer. Two SNPs (172G>T and 135G>C) in the 5'- UTR of RAD51 have been extensively studied for their role in the development of sporadic breast cancer [33]. A few studies demonstrated the relationship between risk of head and neck cancer with the 135G>C SNP while the obtained results were inconsistent. Lu et al., reported that the 172G>T SNP was correlated with decreased risk of HNSCC which was further verified by Gresner et al., [37]. One of the studies reported that the homozygous variants (CC) of RAD51was correlated with a 2.5 fold increased risk of head and neck cancer while heterozygous variants (G/T) was associated with a 1.68 fold increased in head and neck cancer risk in contrast to control [95]. Recently, a meta-analysis explored that the 135G>C SNP was significantly associated with the risk of head and neck cancer [98].

1.7.2 Non-homologous End Joining (NHEJ) Pathway:

It repaired the double DNA strand break without need of homologous DNA sequence template. Imperfect NHEJ results in telomere fusion and translocation which is manifestation of tumors [39]. The key components of the NHEJ system are XRCC4, XRCC5 and XRCC6 and polymorphism in these genes may lead to carcinogenesis. XRCC4 is a critical component of NHEJ pathway and restores the double strand break especially to joints the blunt ends of damaged DNA. The Ser298Ala (rs3734091) SNP was the most commonly explored in comparison to other SNPs and was found to be associated with the risk of oral cancer in Taiwanese populations [40]. They also reported that patients with 247A allele had a 2.04 fold higher chance of developing cancer. Additionally, another study observed that an intron 3 deletion genotype may be correlated with risk of oral cancer

in Taiwanese individuals [85]. A hospital based case control study showed that the increased genetic susceptibility was correlated with the XRCC4 in rural Indian populations [42]. XRCC5 (or Ku80/Ku86) and XRCC6 (or Ku70), are the key players of NHEJ pathway and plays a major role to repair the double strand break during the eukaryotic cell cycles especially at the G0/G1 phase [83]. XRCC5/6 is very important as they maintain the integrity of chromosomes. Several lines of evidence showed that they play a more prominent role in adult mammals in contrast to HR which acts as an alternative repair mechanism for double strand break [44, 45]. Numerous SNPs have been reported for XRCC5 (1092) and XRCC6 (843). A study led by Werbrouck et al., [35] showed that the genotypes of rs2267437 in XRCC6 and rs3835 in XRCC5 were not associated with risk of HNSCC. They also reported that no interaction was observed between these genotypes and genes of alcohol and smoking. Bau et al., [46] observed that the SNP rs5751129 in the promoter region of XRCC6 was correlated with risk of oral cancer in Taiwanese populations. A study conducted by Hsu et al., [77] showed that the rs828907 SNP of XRCC5 but not rs9288518 or rs11685387 genotype was correlated with genetic susceptibility to oral cancer. Recently, a study has been shown that the SNP in XRCC5/6 was correlated with risk of head and cancer in the rural population of India [42]. One of the earlier studies has shown that a combination of XRCC4/5/6 may increase the risk of oral cancer in Taiwanese population [48].

II. Management - Head and Neck Cancer

The management of cancer is very difficult especially in India owing to affordability and availability of treatment modality. Radiotherapy is the most commonly used modality to cure head and neck cancer. In India, surgery with radiotherapy is the most prevalent treatment (36.9%) employed in Mumbai while radiotherapy (>80%) is most commonly employed in Dibrugarh to manage head and neck cancer [99]. Beside this, surgery, chemotherapy, targeted therapy, immunotherapy and combination of these modalities are used to manage the head and neck cancer.

2.1 Surgery

The goal of the surgery is to remove the cancerous tumor and some surrounding tissue around the tumor. Several kinds of surgery are available for head and neck cancer including laser technology, excision, lymph node dissection or dissection and reconstructive or plastic surgery. Laser technology employed to manage the early-stage tumor especially if it occurs in the larynx. Excision is the operation that removes the cancerous tumor as well as surrounding healthy tissue termed as margin. Lymph node dissection is done by the doctors especially when doctors suspect that cancer has spread. Reconstructive surgery is employed when a large proportion of tissue is needed to remove from the cancer patients like removal of jaw, pharynx, skin and tongue. Reconstructive surgeries restore the normal appearance of cancer patients. In case of head and neck cancer, surgical side effects are disfigurement of face, impaired speech, reduced thyroid function, permanent loss of voice and hearing. In addition to this, lymphedema can occur in case of removal of the larynx.

2.2 Radiotherapy

It is the most prevalent modality used to treat various cancers. It is the use of X-rays of high energy or other particles to destroy the cancerous cells. Radiation therapy may be employed in different ways to manage the head and neck cancer like help to cure the disease or reduce the associated symptoms. It may be used solely or in combination with other therapy like chemotherapy or surgery. The prevalent radiation therapy to cure head and neck cancer is external beam radiation therapy (EBRT). IMRT (intensity-modulated radiation therapy) and proton therapy are the subtypes of EBRT. Proton therapy is not employed in case of head and neck cancer. IMRT uses advanced technology that enhances the accuracy of beam radiation only at the cancerous tumor cells. Complications associated with radiation therapy including skin irritation, hypothyroidism, Xerostomia, lymphedema, mouth and throat sores, fatigue and nausea.

2.3 Chemotherapy

It is the systemic use of drugs to damage the cancerous tumor cells by inhibiting the tumor cells from proliferation and differentiation. A chemotherapy schedule comprises a specific number of cycles for a particular period. Sometimes medical oncologists recommend this as a part of radiation therapy because radiation enhances the sensitivity of tumor cells. Cisplatin is the standard drug employed against head and neck cancer. Other commonly used chemotherapy drugs are cisplatin, carboplatin, fluorouracil, paclitaxel, methotrexate and docetaxel. Cetuximab is the recently approved drug that is used in case of head and neck cancer. Complications associated with chemotherapy are nausea, fatigue, loss appetite, loss of hair, and diarrhea which depends upon the individual and dose of drugs.

2.4 Targeted Therapy

It is the newest form of drug therapy and allows doctors to treat the individual tumor having specific genetic differences which is identified by genomic testing. This therapy targets the specific proteins, genes and tissue microenvironment around the tumor cells especially those involved in growth and survival of tumor cells. Due to positional heterogeneity, all tumors do not have similar targets. EGFR (epidermal growth factor receptor) is the only target approved for head and neck cancer. Cetuximab, zalutumumab, panitumumab and nimotuzumab are the EGFR monoclonal antibodies while gefitinib, lapatinib, erlotinib, dacomitinib and afatinib are the EGFR tyrosine kinase inhibitor (TKI) employed to cure the head and neck cancer.

2.5 Immunotherapy

It is also known as biological therapy because it enhances the natural defense system of the patients to fight cancer. There are two checkpoint inhibitors (Pembrolizumab and nivolumab) approved by the US-FDA as immunotherapy drugs for the treatment of metastatic head and neck cancer. Both drugs target the PD1-protein reside on immune cells. Common complications associated with immunotherapy are flu-like symptoms, weight changes, diarrhea, and skin reactions.

2.6 Combination Therapy

Most of the head and neck cancers can be treated if they are diagnosed at an early stage. If the head and neck cancer enter into the severe stage and affects the quality of life of the patients, then doctors employ a combination therapy to cure the cancer.

III. CONCLUSION

Genomic material of humans is constantly exposed to exogenous and endogenous factors. Malfunction in the DNA repair genes increase the instability of genomic material which is a hallmark of cancer. Several published studies explored the role of DNA repair genes to know the genetic susceptibility to head and neck cancer while still results are inconsistent. Unveiling the role of molecular players that interplay between different DNA repair pathways may be helpful to develop the novel therapeutic drugs. In spite of this, large international multi-centric studies are needed to know the mechanism behind the ethnic genetic variability among the individuals of different countries as well as to shed a light on the molecular signatures behind the positional and temporal heterogeneity features of tumor cells related to head and neck cancer.

REFERENCES

[1]. Parkin DM, Pisani P, Ferlay J. Global cancer statistics. CA: a cancer journal for clinicians. Jan, 1999;49 (1): 33-64.
[2]. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA: a cancer journal for clinicians. Jan, 2015;5;65(1):5-29.
[3]. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: a cancer journal for clinicians. Nov, 2018;68(6):394-424.
[4]. Argiris A, Karamouzis MV, Raben D, Ferris RL. Head and neck cancer. The Lancet. May, 2008;17;371(9625):1695-709.
[5]. Leemans CR, Braakhuis BJ, Brakenhoff RH. The molecular biology of head and neck cancer. Nature reviews cancer. Jan, 2011;11(1):9-22.
[6]. Kubrak C, Olson K, Baracos VE. The head and neck symptom checklist©: an instrument to evaluate nutrition impact symptoms effect on energy intake and weight loss. Supportive care in cancer. Nov, 2013;21(11):3127-36.
[7]. Klein JD, Grandis JR. The molecular pathogenesis of head and neck cancer. Cancer biology & therapy. Jan, 2010;1;9(1):1-7.
[8]. Goon PK, Stanley MA, Ebmeyer J, Steinsträsser L, Upile T, Jerjes W, Bernal-Sprekelsen M, Görner M, Sudhoff HH. HPV & head and neck cancer: a descriptive update. Head & neck oncology. Dec, 2009;1(1):1-8.
[9]. Hashibe M, Boffetta P, Zaridze D, Shangina O, Szeszenia-Dabrowska N, Mates D, Janout V, Fabiánová E, Bencko V, Moullan N, Chabrier A. Evidence for an important role of alcohol-and aldehyde-metabolizing genes in cancers of the upper aerodigestive tract. Cancer Epidemiology and Prevention Biomarkers. Apr, 2006;1;15(4):696-703.
[10]. Boffetta P, Hecht S, Gray N, Gupta P, Straif K. Smokeless tobacco and cancer. The lancet oncology. Jul, 2008;1;9(7):667-75.
[11]. Negri E, Boffetta P, Berthiller J, Castellsague X, Curado MP, Maso LD, Daudt AW, Fabianova E, Fernandez L, Wünsch-Filho V, Franceschi S. Family history of cancer: pooled analysis in the International Head and Neck Cancer Epidemiology Consortium. International journal of cancer. Jan, 2009;15;124(2):394-401.
[12]. Siegel; Kimberly D. Miller; Ahmedin Jemal RL. Cancer statistics,CA: A Cancer Journal for Clinicians. 2015(1).
[13]. Ruwali M, Parmar D. Association of functionally important polymorphisms in cytochrome P450s with squamous cell carcinoma of head and neck.

[14]. Johnson DE, Burtness B, Leemans CR, Lui VW, Bauman JE, Grandis JR. Head and neck squamous cell carcinoma. Nature reviews Disease primers. Nov, 2020;26;6(1):1-22.
[15]. Viswanathan H, Wilson JA. Alcohol–the neglected risk factor in head and neck cancer. Clinical Otolaryngology & Allied Sciences. Aug, 2004;29(4):295-300.
[16]. Mathur P, Sathishkumar K, Chaturvedi M, Das P, Sudarshan KL, Santhappan S, Nallasamy V, John A, Narasimhan S, Roselind FS, ICMR-NCDIR-NCRP Investigator Group. Cancer statistics: report from national cancer registry programme, India. JCO Global Oncology. Jul, 2020;6:1063-75.
[17]. Tubbs A, Nussenzweig A. Endogenous DNA damage as a source of genomic instability in cancer. Cell. Feb, 2017; 9;168(4):644-56.
[18]. De Bont R, Van Larebeke N. Endogenous DNA damage in humans: a review of quantitative data. Mutagenesis. May, 2004 1;19(3):169-85.
[19]. Pfeifer GP, Denissenko MF, Olivier M, Tretyakova N, Hecht SS, Hainaut P. Tobacco smoke carcinogens, DNA damage and p53 mutations in smoking-associated cancers. Oncogene. Oct, 2002;21(48):7435-51.
[20]. Zhong Y, Carmella SG, Upadhyaya P, Hochalter JB, Rauch D, Oliver A, Jensen J, Hatsukami D, Wang J, Zimmerman C, Hecht SS. Immediate consequences of cigarette smoking: rapid formation of polycyclic aromatic hydrocarbon diol epoxides. Chemical research in toxicology. Feb, 2011;18;24(2):246-52.
[21]. Hoeijmakers JH. Genome maintenance mechanisms for preventing cancer. nature. May, 2001;411(6835):366-74.
[22]. Yu HP, Zhang XY, Wang XL, Shi LY, Li YY, Li F, Su YH, Wang YJ, Lu B, Sun X, Lu WH. DNA repair gene XRCC1 polymorphisms, smoking, and esophageal cancer risk. Cancer Detection and Prevention. Jul, 2004;1;28(3):194-9.
[23]. Wood RD, Mitchell M, Sgouros J, Lindahl T. Human DNA repair genes. Science. Feb 16, 2001;291(5507):1284-9.
[24]. Foulkes WD, Brunet JS, Sieh W, Black MJ, Shenouda G, Narod SA. Familial risks of squamous cell carcinoma of the head and neck: retrospective case-control study. Bmj. Sep, 1996;21;313(7059):716-21.
[25]. Sancar A. DNA repair in humans. Annual review of genetics. Dec, 1995;29(1):69-105.
[26]. Li D, Wang M, Cheng L, Spitz MR, Hittelman WN, Wei Q. In vitro induction of benzo (a) pyrene diol epoxide-DNA adducts in peripheral lymphocytes as a susceptibility marker for human lung cancer. Cancer research. Aug, 1996;15;56(16):3638-41.
[27]. Sturgis EM, Castillo EJ, Li L, Zheng R, Eicher SA, Clayman GL, Strom SS, Spitz MR, Wei Q. Polymorphisms of DNA repair gene XRCC1 in squamous cell carcinoma of the head and neck. Carcinogenesis. Nov 1, 1999;20(11):2125-9.
[28]. Sturgis EM, Zheng R, Li L, Castillo EJ, Eicher SA, Chen M, Strom SS, Spitz MR, Wei Q. XPD/ERCC2 polymorphisms and risk of head and neck cancer: a case-control analysis. Carcinogenesis. Dec 1, 2000;21(12):2219-23.
[29]. Puga A, Nebert DW, McKinnon RA, Menon AG. Genetic polymorphisms in human drug-metabolizing enzymes: potential uses of reverse genetics to identify genes of toxicological relevance. Critical reviews in toxicology. Jan 1, 1997;27(2):199-222.
[30]. Ryberg D, Skaug V, Hewer A, Phillips DH, Harries LW, Wolf CR, Ogreid D, Ulvik A, Vu P, Haugen A. Genotypes of glutathione transferase M1 and P1 and their significance for lung DNA adduct levels and cancer risk. Carcinogenesis. Jul 1, 1997;18(7):1285-9.
[31]. Chen K, Zhao H, Hu Z, Wang LE, Zhang W, Sturgis EM, Wei Q. CASP3 polymorphisms and risk of squamous cell carcinoma of the head and neck. Clinical Cancer Research. Oct 1, 2008;14(19):6343-9.
[32]. Essers PB, van der Heijden M, Verhagen CV, Ploeg EM, de Roest RH, Leemans CR, Brakenhoff RH, van den Brekel MW, Bartelink H, Verheij M, Vens C. Drug sensitivity prediction models reveal a link between DNA repair defects and poor prognosis in HNSCC. Cancer research. Nov 1, 2019;79(21):5597-611.
[33]. Wang M, Chu H, Zhang Z, Wei Q. Molecular epidemiology of DNA repair gene polymorphisms and head and neck cancer. Journal of biomedical research. May 27, 2013; (3):179.
[34]. Khlifi R, Rebai A, Hamza-Chaffai A. Polymorphisms in human DNA repair genes and head and neck squamous cell carcinoma. Journal of genetics. Dec 1, 2012;91(3):375-84.
[35]. Broughton BC, Steingrimsdottir H, Lehmann AR. Five polymorphisms in the coding sequence of the xeroderma pigmentosum group D gene. Mutation Research/DNA Repair. Feb 15, 1996;362(2):209-11.
[36]. Shen MR, Jones IM, Mohrenweiser H. Nonconservative amino acid substitution variants exist at polymorphic frequency in DNA repair genes in healthy humans. Cancer research. Feb 15, 1998;58(4):604-8.
[37]. Olshan AF, Watson MA, Weissler MC, Bell DA. XRCC1 polymorphisms and head and neck cancer. Cancer letters. Apr 25, 2002;178(2):181-6.
[38]. Sturgis EM, Castillo EJ, Li L, Zheng R, Eicher SA, Clayman GL, Strom SS, Spitz MR, Wei Q. Polymorphisms of DNA repair gene XRCC1 in squamous cell carcinoma of the head and neck. Carcinogenesis. Nov 1, 1999;20(11):2125-9.
[39]. Tae K, Lee HS, Park BJ, Park CW, Kim KR, Cho HY, Kim LH, Park BL, Shin HD. Association of DNA repair gene XRCC1 polymorphisms with head and neck cancer in Korean population. International journal of cancer. Sep 20, 2004;111(5):805-8.
[40]. Rich T, Allen RL, Wyllie AH. Defying death after DNA damage. Nature. Oct, 2000; 407(6805):777-83.
[41]. Hakem R. DNA-damage repair; the good, the bad, and the ugly. The EMBO journal. Feb 20, 2008;27(4):589-605.

[42]. Dianov GL, Hübscher U. Mammalian base excision repair: the forgotten archangel. Nucleic acids research. Apr 1, 2013;41(6):3483-90.
[43]. Wilson III DM, Kim D, Berquist BR, Sigurdson AJ. Variation in base excision repair capacity. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. Jun 3, 2011;711(1-2):100-12.
[44]. Dianov GL, Souza-Pinto N, Nyaga SG, Thybo T, Stevnsner T, Bohr VA. Base excision repair in nuclear and mitochondrial DNA. Progress in nucleic acid research and molecular biology. Jan 1, 2001;68:285-97.
[45]. Cho EY, Hildesheim A, Chen CJ, Hsu MM, Chen IH, Mittl BF, Levine PH, Liu MY, Chen JY, Brinton LA, Cheng YJ. Nasopharyngeal carcinoma and genetic polymorphisms of DNA repair enzymes XRCC1 and hOGG1. Cancer Epidemiology and Prevention Biomarkers. Oct 1, 2003;12(10):1100-4.
[46]. Pawlowska E, Janik-Papis K, Rydzanicz M, Zuk K, Kaczmarczyk D, Olszewski J, Szyfter K, Blasiak J, Morawiec-Sztandera A. The Cys326 allele of the 8-oxoguanine DNA N-glycosylase 1 gene as a risk factor in smoking-and drinking-associated larynx cancer. The Tohoku journal of experimental medicine. 2009;219(4):269-75.
[47]. Sliwinski T, Przybylowska K, Markiewicz L, Rusin P, Pietruszewska W, Zelinska-Blizniewska H, Olszewski J, Morawiec-Sztandera A, Mlynarski W, Majsterek I. MUTYH Tyr165Cys, OGG1 Ser326Cys and XPD Lys751Gln polymorphisms and head neck cancer susceptibility: a case control study. Molecular biology reports. Feb 1, 2011;38(2):1251-61.
[48]. Leu M, Riebeling T, Dröge LH, Hubert L, Guhlich M, Wolff HA, Brockmöller J, Gaedcke J, Rieken S, Schirmer MA. 8-Oxoguanine DNA Glycosylase (OGG1) Cys326 Variant: Increased Risk for Worse Outcome of Patients with Locally Advanced Rectal Cancer after Multimodal Therapy. Cancers. Jan 13, 2021;(11):2805
[49]. Elahi A, Zheng Z, Park J, Eyring K, McCaffrey T, Lazarus P. The human OGG1 DNA repair enzyme and its association with orolaryngeal cancer risk. Carcinogenesis. Jul 1, 2002;23(7):1229-34.
[50]. Izumi T, Hazra TK, Boldogh I, Tomkinson AE, Park MS, Ikeda S, Mitra S. Requirement for human AP endonuclease 1 for repair of 3′-blocking damage at DNA single-strand breaks induced by reactive oxygen species. Carcinogenesis. Jul 1, 2000;21(7):1329-34.
[51]. Fortini P, Pascucci B, Parlanti E, D'errico M, Simonelli V, Dogliotti E. The base excision repair: mechanisms and its relevance for cancer susceptibility. Biochimie. Nov 1, 2003;85(11):1053-71.
[52]. Lu J, Zhang S, Chen D, Wang H, Wu W, Wang X, Lei Y, Wang J, Qian J, Fan W, Hu Z. Functional characterization of a promoter polymorphism in APE1/Ref-1 that contributes to reduced lung cancer susceptibility. The FASEB Journal. Oct 23, 2009;(10):3459-69.
[53]. Lo YL, Jou YS, Hsiao CF, Chang GC, Tsai YH, Su WC, Chen KY, Chen YM, Huang MS, Hu CY, Chen CJ. A polymorphism in the APE1 gene promoter is associated with lung cancer risk. Cancer Epidemiology and Prevention Biomarkers. Jan 1, 2009;18(1):223-9.
[54]. Hu JJ, Smith TR, Miller MS, Mohrenweiser HW, Golden A, Case LD. Amino acid substitution variants of APE1 and XRCC1 genes associated with ionizing radiation sensitivity. Carcinogenesis. Jun 1, 2001;22(6):917-22.
[55]. Li C, Hu Z, Lu J, Liu Z, Wang LE, El-Naggar AK, Sturgis EM, Spitz MR, Wei Q. Genetic polymorphisms in DNA base-excision repair genes ADPRT, XRCC1, and APE1 and the risk of squamous cell carcinoma of the head and neck. Cancer: Interdisciplinary International Journal of the American Cancer Society. Aug 15, 2007;110(4):867-75.
[56]. Matullo G, Dunning AM, Guarrera S, Baynes C, Polidoro S, Garte S, Autrup H, Malaveille C, Peluso M, Airoldi L, Veglia F. DNA repair polymorphisms and cancer risk in non-smokers in a cohort study. Carcinogenesis. May 1, 2006;27(5):997-1007.
[57]. Gu D, Wang M, Wang M, Zhang Z, Chen J. The DNA repair gene APE1 T1349G polymorphism and cancer risk: a meta-analysis of 27 case–control studies. Mutagenesis. Nov 1, 2009;24(6):507-12.
[58]. Pratesi N, Mangoni M, Mancini I, Paiar F, Simi L, Livi L, Cassani S, Buglione M, Grisanti S, Almici C, Polli C. Association between single nucleotide polymorphisms in the XRCC1 and RAD51 genes and clinical radiosensitivity in head and neck cancer. Radiotherapy and Oncology. Jun 1, 2011;99(3):356-61.
[59]. Kowalski M, Przybylowska K, Rusin P, Olszewski J, Morawiec-Sztandera A, Bielecka-Kowalska A, Pietruszewska W, Mlynarski W, Janusz S, Majsterek I. Genetic polymorphisms in DNA base excision repair gene XRCC1 and the risk of squamous cell carcinoma of the head and neck. Journal of Experimental & Clinical Cancer Research. Dec 28, 2009;(1):1-7.
[60]. Kang SY, Lee KG, Lee W, Shim JY, Ji SI, Chung KW, Chung YK, Kim NK. Polymorphisms in the DNA repair gene XRCC1 associated with basal cell carcinoma and squamous cell carcinoma of the skin in a Korean population. Cancer science. May, 2007;98(5):716-20.
[61]. Hu Z, Ma H, Chen F, Wei Q, Shen H. XRCC1 polymorphisms and cancer risk: a meta-analysis of 38 case-control studies. Cancer Epidemiology and Prevention Biomarkers. Jul 1, 2005;14(7):1810-8.
[62]. Xia S, Wu S, Wang M. The Association Between the XRCC1 Arg399Gln Polymorphism and the Risk of Head and Neck Cancer: An Updated Meta-Analysis Including 14586 Subjects.

Technology in Cancer Research & Treatment. Jul 16, 2021;20:15330338211033060.

[63]. Kiuru A, Lindholm C, Heilimo I, Ceppi M, Koivistoinen A, Ilus T, Hirvonen A, Norppa H, Salomaa S. Influence of DNA repair gene polymorphisms on the yield of chromosomal aberrations. Environmental and molecular mutagenesis. Oct, 2005;46(3):198-205.

[64]. Dutta D, Abarna R, Shubham M, Subbiah K, Duraisamy S, Chinnusamy R, Anbalagan M. Effect of Arg399Gln single-nucleotide polymorphism in XRCC1 gene on survival rate of Indian squamous cell head-and-neck cancer patients. Journal of Cancer Research and Therapeutics. Jul 1, 2020;16(3):551.

[65]. Applebaum KM, McClean MD, Nelson HH, Marsit CJ, Christensen BC, Kelsey KT. Smoking modifies the relationship between XRCC1 haplotypes and HPV16-negative head and neck squamous cell carcinoma. International journal of cancer. Jun 1, 2009;124(11):2690-6.

[66]. Sugasawa K. Regulation of damage recognition in mammalian global genomic nucleotide excision repair. Mutation Research/Fundamental and Molecular Mechanisms of Mutagenesis. Mar 1, 2010;685(1-2):29-37.

[67]. Zeng-Rong N, Paterson J, Alpert L, Tsao MS, Viallet J, Alaoui-Jamali MA. Elevated DNA repair capacity is associated with intrinsic resistance of lung cancer to chemotherapy. Cancer research. Nov 1, 1995;55(21):4760-4.

[68]. Wei Q, Cheng L, Xie K, Bucana CD, Dong Z. Direct correlation between DNA repair capacity and metastatic potential of K-1735 murine melanoma cells. Journal of investigative dermatology. Jan 1, 1997;108(1):3-6.

[69]. Volker M, Moné MJ, Karmakar P, van Hoffen A, Schul W, Vermeulen W, Hoeijmakers JH, van Driel R, van Zeeland AA, Mullenders LH. Sequential assembly of the nucleotide excision repair factors in vivo. Molecular cell. Jul 1, 2001;8(1):213-24.

[70]. Dylawerska A, Barczak W, Wegner A, Golusinski W, Suchorska WM. Association of DNA repair genes polymorphisms and mutations with increased risk of head and neck cancer: a review. Medical Oncology. Dec 1, 2017;34(12):197.

[71]. Psyrri A, Gkotzamanidou M, Papaxoinis G, Krikoni L, Economopoulou P, Kotsantis I, Anastasiou M, Souliotis VL. The DNA damage response network in the treatment of head and neck squamous cell carcinoma. ESMO open. Apr 1, 2021;6(2):100075.

[72]. Park JY, Park SH, Choi JE, Lee SY, Jeon HS, Cha SI, Kim CH, Park JH, Kam S, Park RW, Kim IS. Polymorphisms of the DNA repair gene xeroderma pigmentosum group A and risk of primary lung cancer. Cancer Epidemiology and Prevention Biomarkers. Oct 1, 2002;11(10):993-7.

[73]. Wu X, Zhao H, Wei Q, Amos CI, Zhang K, Guo Z, Qiao Y, Hong WK, Spitz MR. XPA polymorphism associated with reduced lung cancer risk and a modulating effect on nucleotide excision repair capacity. Carcinogenesis. Mar 1, 2003;24(3):505-9.

[74]. Sugimura T, Kumimoto H, Tohnai I, Fukui T, Matsuo K, Tsurusako S, Mitsudo K, Ueda M, Tajima K, Ishizaki K. Gene–environment interaction involved in oral carcinogenesis: molecular epidemiological study for metabolic and DNA repair gene polymorphisms. Journal of oral pathology & medicine. Jan 3, 2006;5(1):11-8.

[75]. Bau D, Tsai M, Huang C, Lee C, Tseng H, Lo Y, Tsai Y, Tsai F. Relationship between polymorphisms of nucleotide excision repair genes and oral cancer risk in Taiwan: evidence for modification of smoking habit. Chinese Journal of Physiology. Dec 31, 2007;50(6):294.

[76]. Abbasi R, Ramroth H, Becher H, Dietz A, Schmezer P, Popanda O. Laryngeal cancer risk associated with smoking and alcohol consumption is modified by genetic polymorphisms in ERCC5, ERCC6 and RAD23B but not by polymorphisms in five other nucleotide excision repair genes. International journal of cancer. Sep 15, 2009;125(6):1431-9.

[77]. Jelonek K, Gdowicz-Kłosok A, Pietrowska M, Borkowska M, Korfanty J, Rzeszowska-Wolny J, Widłak P. Association between single-nucleotide polymorphisms of selected genes involved in the response to DNA damage and risk of colon, head and neck, and breast cancers in a Polish population. Journal of applied genetics. Sep, 2010;51(3):343-52.

[78]. Liu J, Zhang Z, Cao XL, Lei DP, Wang ZQ, Jin T, Pan XL. XPA A23G polymorphism and susceptibility to cancer: a meta-analysis. Molecular biology reports. Jun, 2012;39(6):6791-9.

[79]. Huang WY, Berndt SI, Kang D, Chatterjee N, Chanock SJ, Yeager M, Welch R, Bresalier RS, Weissfeld JL, Hayes RB. Nucleotide excision repair gene polymorphisms and risk of advanced colorectal adenoma: XPC polymorphisms modify smoking-related risk. Cancer Epidemiology and Prevention Biomarkers. Feb 1, 2006;15(2):306-11.

[80]. Shen H, Sturgis EM, Khan SG, Qiao Y, Shahlavi T, Eicher SA, Xu Y, Wang X, Strom SS, Spitz MR, Kraemer KH. An intronic poly (AT) polymorphism of the DNA repair gene XPC and risk of squamous cell carcinoma of the head and neck: a case-control study. Cancer research. Apr 15, 2001;61(8):3321-5.

[81]. An J, Liu Z, Hu Z, Li G, Wang LE, Sturgis EM, El-Naggar AK, Spitz MR, Wei Q. Potentially functional single nucleotide polymorphisms in the core nucleotide excision repair genes and risk of squamous cell carcinoma of the head and neck. Cancer Epidemiology and Prevention Biomarkers. Aug 1, 2007;16(8):1633-8.

[82]. Yang M, Kang MJ, Choi Y, Kim CS, Lee SM, Park CW, Lee HS, Tae K. Associations between XPC expression, genotype, and the risk of head and neck cancer. Environmental and molecular mutagenesis. 2005;45(4):374-9.

[83]. Yadav SK, Singh S, Gupta S, Bhatt ML, Mishra DP, Roy D, Sanyal S. Modulation of risk of squamous cell carcinoma head and neck in North Indian population with polymorphisms in

xeroderma pigmentosum complementation Group C gene. Journal of cancer research and therapeutics. Apr 1, 2018;14(3):651.

[84]. Wood RD. Nucleotide excision repair in mammalian cells. Journal of Biological Chemistry. Sep 19, 1997;272(38):23465-8.

[85]. Zhang L, Wang J, Xu L, Zhou J, Guan X, Jiang F, Wu Y, Fan W. Nucleotide excision repair gene ERCC1 polymorphisms contribute to cancer susceptibility: a meta-analysis. Mutagenesis. Jan 1, 2012;27(1):67-76.

[86]. Li Y, Gu S, Wu Q, Li Y, Fu X, Mao Y, Huang Y, Xie Y. No association of ERCC1 C8092A and T19007C polymorphisms to cancer risk: a meta-analysis. European journal of human genetics. Sep, 2007;15(9):967-73.

[87]. Yang ZH, Dai Q, Kong XL, Yang WL, Zhang L. Association of ERCC1 polymorphisms and susceptibility to nasopharyngeal carcinoma. Molecular Carcinogenesis: Published in cooperation with the University of Texas MD Anderson Cancer Center. Mar, 2009;48(3):196-201.

[88]. Yang M, Kim WH, Choi Y, Lee SH, Kim KR, Lee HS, Tae K. Effects of ERCC1 expression in peripheral blood on the risk of head and neck cancer. European journal of cancer prevention. Jun 1, 2006;15(3):269-73.

[89]. Sturgis EM, Dahlstrom KR, Spitz MR, Wei Q. DNA repair gene ERCC1 and ERCC2/XPD polymorphisms and risk of squamous cell carcinoma of the head and neck. Archives of Otolaryngology–Head & Neck Surgery. Sep 1, 2002;128(9):1084-8.

[90]. Tejasvi MA, Maragathavalli G, Putcha UK, Ramakrishna M, Vijayaraghavan R, Avinash CA. Impact of ERCC1 gene polymorphisms on response to cisplatin based therapy in oral squamous cell carcinoma (OSCC) patients. Indian Journal of Pathology and Microbiology. Oct 1, 2020;63(4):538.

[91]. Hou SM, Fält S, Angelini S, Yang K, Nyberg F, Lambert B, Hemminki K. The XPD variant alleles are associated with increased aromatic DNA adduct level and lung cancer risk. carcinogenesis. Apr 1, 2002;23(4):599-603.

[92]. Benhamou S, Sarasin A. ERCC2/XPD gene polymorphisms and cancer risk. Mutagenesis. Nov 1, 2002;17(6):463-9.

[93]. Yuan H, Niu YM, Wang RX, Li HZ, Chen N. Association between XPD Lys751Gln polymorphism and risk of head and neck cancer: a meta-analysis. Genet Mol Res. Nov 22, 2011;10(4):3356-64.

[94]. Wang M, Chu H, Zhang Z, Wei Q. Molecular epidemiology of DNA repair gene polymorphisms and head and neck cancer. Journal of biomedical research. May, 2013;27(3):179.

[95]. Krupa R, Kasznicki J, Gajecka M, Rydzanicz M, Kiwerska K, Kaczmarczyk D, Olszewski J, Szyfter K, Blasiak J, Morawiec-Sztandera A. Polymorphisms of the DNA repair genes XRCC1 and ERCC4 are not associated with smoking-and drinking-dependent larynx cancer in a Polish population. Experimental oncology. 2011.

[96]. Shi TY, He J, Qiu LX, Zhu ML, Wang MY, Zhou XY, Han J, Yu H, Zang RY, Wei Q. Association between XPF polymorphisms and cancer risk: a meta-analysis. PLoS One. Jul 2, 2012;7(7):e38606.

[97]. Kiyohara C, Yoshimasu K. Genetic polymorphisms in the nucleotide excision repair pathway and lung cancer risk: a meta-analysis. International journal of medical sciences. 2007;4(2):59.

[98]. Yuan H, Li H, Ma H, Niu Y, Wu Y, Zhang S, Hu Z, Shen H, Chen N. Genetic polymorphisms in key DNA repair genes and risk of head and neck cancer in a Chinese population. Experimental and therapeutic medicine. Apr 1, 2012;3(4):719-24.

[99]. Manuguerra M, Matullo G, Veglia F, Autrup H, Dunning AM, Garte S, Gormally E, Malaveille C, Guarrera S, Polidoro S, Saletta F. Multi-factor dimensionality reduction applied to a large prospective investigation on gene–gene and gene–environment interactions. Carcinogenesis. Feb 1, 2007;28(2):414-22.

[100]. Ito E, Yanagisawa Y, Iwahashi Y, Suzuki Y, Nagasaki H, Akiyama Y, Sugano S, Yuasa Y, Maruyama K. A Core Promoter and a Frequent Single-Nucleotide Polymorphism of the Mismatch Repair GenehMLH1. Biochemical and biophysical research communications. Mar 24, 1999;256(3):488-94.