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REVIEW

ERCC1 and *XRCC1* as biomarkers for lung and head and neck cancer

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Abstract: Advanced stage non-small cell lung cancer and head and neck squamous cell carcinoma are both treated with DNA damaging agents including platinum-based compounds and radiation therapy. However, at least one quarter of all tumors are resistant or refractory to these genotoxic agents. Yet the agents are extremely toxic, leading to undesirable side effects with potentially no benefit. Alternative therapies exist, but currently there are no tools to predict whether the first-line genotoxic agents will work in any given patient. To maximize therapeutic success and limit unnecessary toxicity, emerging clinical trials aim to inform personalized treatments tailored to the biology of individual tumors. Worldwide, significant resources have been invested in identifying biomarkers for guiding the treatment of lung and head and neck cancer. DNA repair proteins of the nucleotide excision repair pathway (*ERCC1*) and of the base excision repair pathway (*XRCC1*), which are instrumental in clearing DNA damage caused by platinum drugs and radiation, have been extensively studied as potential biomarkers of clinical outcomes in lung and head and neck cancers. The results are complex and contradictory. Here we summarize the current status of single nucleotide polymorphisms, mRNA, and protein expression of *ERCC1* and *XRCC1* in relation to cancer risk and patient outcomes.

Keywords: nucleotide excision repair, base excision repair, DNA damage, DNA repair, chemotherapy, NSCLC, HNSCC, single nucleotide polymorphism

Introduction

Lung cancer is the second most common cancer in the USA and is the leading cause of cancer-related death.[1] Based on the predicted response to treatment and known risk factors, lung cancers are categorized in two groups: small cell and non-small cell lung cancers (NSCLC). NSCLC are more frequent, and smoking is a risk factor. Histologically, NSCLC are composed mainly of adenocarcinoma and, to a lesser degree, of squamous cell carcinoma (SCC) and large cell carcinoma. Treatment varies based on clinical stage. Early stage NSCLC is treated with surgery, while loco-regionally advanced and metastatic cancers are treated with multidrug systemic chemotherapy, which often includes a platinum compound.[2]

Head and neck cancers are similar to NSCLC in many respects, although they are less common, representing the eighth most frequent type of cancer in the USA.[1] Smoking is a recognized risk factor for head and neck cancers, like for NSCLC. Pathologically, cancers of the aerodigestive tract are mostly head and neck squamous cell carcinoma (HNSCC). As for NSCLC, early stage HNSCC is successfully treated with surgery, while treatment of loco-regionally advanced tumors includes systemic therapy.[2–4] Frequently, concomitant radiotherapy and chemotherapy with a platinum-based DNA

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damaging agent (cisplatin or carboplatin) is used, either as primary treatment or as adjuvant post-operative therapy. Alternative systemic treatments that do not rely upon DNA damage, such as taxanes, base analogs, and anti-metabolites can also be used.[4] However, currently we do not have the tools to predict which patients will respond best to the various possible therapies.

To maximize treatment success of NSCLC and HNSCC, and to reduce unnecessary toxicity, there is great demand for identifying biomarkers that predict clinical outcomes prospectively. The goal is to measure validated biomarker(s) in individual tumors to probe the biology of each tumor and predict whether it is likely to be vulnerable to genotoxic agents such radiation and platinum drugs. This would enable identification of patients likely to be resistant to these modalities, allowing use of alternative therapies, preventing unnecessary toxic side-effects, and improving clinical outcomes.

Choosing a biomarker

Biomarkers in DNA repair pathways

DNA repair proteins are obvious candidate biomarkers for predicting how tumors will respond to genotoxic stress. The prediction is that overexpression of DNA repair proteins in tumors could mediate resistance to genotoxic therapies and therefore poor outcomes. In turn, persons with inherited defects in DNA repair mechanisms are frequently exquisitely hypersensitive to radiation and/or genotoxic agents. This is true of patients with ataxia telangiectasia (AT), ataxia telangiectasia-like disorder, severe combined immunodeficiency, Ligase IV syndrome, Rothmund–Thompson syndrome, Seckel syndrome, Werner syndrome, Nijmegen breakage syndrome, all due to defective repair of double-strand breaks (DSBs)[5] or stalled replication forks.[6] It is also true of patients with Fanconi anemia caused by defective repair of DNA interstrand crosslinks (ICLs) and patients with xeroderma pigmentosum due to a defect in nucleotide excision repair (NER) of helix-distorting DNA adducts.[7,8] Since NSCLC and HNSCC are treated with cisplatin and radiation therapy, it is logical to predict that patients with reduced DSB repair, single-strand break (SSB) repair, ICL repair, or NER due to polymorphisms affecting the expression or function of DNA repair proteins might be most responsive to DNA damaging agents.

ERCC1-XPF repair endonuclease

ERCC1 is an attractive candidate biomarker. ERCC1 partners with XPF to form a bi-partite nuclease that is essential for NER and ICL repair, and participates in DSB repair (Figure 1).[9–12]

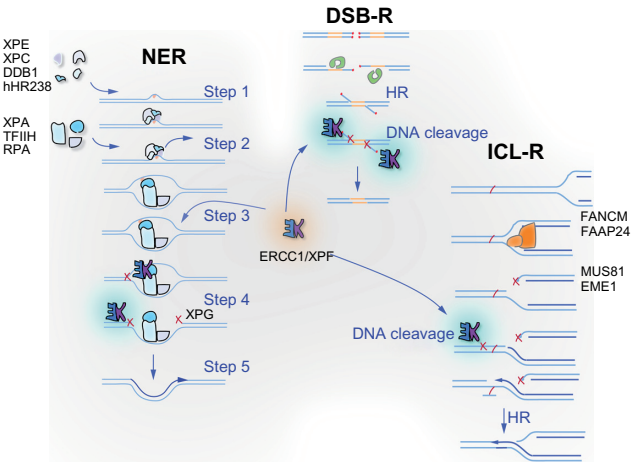

Figure 1 *ERCC1* and its obligate binding partner XPF are involved in multiple DNA repair pathways. ERCC1-XPF heterodimer is an endonuclease that cuts one strand of DNA at a double-strand:single-strand junction. It is critical for nucleotide excision repair (NER) of bulky chemical DNA adducts like cisplatin intrastrand crosslinks, the repair of double-strand breaks that cannot be directly ligated back together like those induced by ionizing radiation, and the repair of interstrand crosslinks (ICLs). In NER (represented on the left), adducts that cause distortion of the DNA double helix are detected by XPC-hHR23B, in some cases with the assistance of XPE-DDB1 (Step 1). These complexes recruit of TFIIH, which unwinds the DNA around the adduct and XPA and RPA, which stabilize the open complex (Step 2). XPA recruits ERCC1-XPF to cut the damaged strand 5′ to the adduct (Step 3), while TFIIH recruits a second endonuclease XPG to cut 3′ of the lesion (Step 4). The damaged base is removed as part of a single-stranded oligonucleotide. The replication machinery uses the 3′-OH created by ERCC1-XPF incision to prime DNA synthesis to fill the gap (Step 5). After ligation, the integrity of the DNA is fully restored. In double-strand breaks (DSB) repair (represented in the middle), two broken ends can be spliced together if they have long patches of sequence homology via homologous recombination (labeled HR) or if they have small patches of homology, known as microhomology, very close to the broken ends via alternative end-joining. In both cases, ERCC1-XPF is needed to remove 3′ single-stranded flaps of non-homologous sequence at the ends of the breaks (labeled DNA cleavage) to allow sealing of the spliced ends by a DNA ligase. ICLs (represented on the right) are predominantly repaired during S phase of the cell cycle. ICLs are an absolute block to replication and when encountered by the replication machinery lead to the collapse of the replication fork and creation of a DSB. This DSB cannot be repaired until ERCC1-XPF cuts near the ICL to release it from one strand (DNA cleavage), allowing bypass of the adduct by a translesion polymerase such as REV1/Polζ.

Platinum-based chemotherapy drugs react with DNA to induce adducts that affect one strand of DNA (monoadducts and intrastrand crosslinks), which are repaired by NER, as well as adducts that affect both strands (ICLs), which are repaired by a distinct DNA repair mechanism: ICL repair.[13–15] Because ERCC1-XPF is unique in being required for both NER and ICL repair pathways, it is the only enzyme required for removal of all types of DNA lesions caused by cisplatin and carboplatin. In addition, it facilitates the repair of DNA lesions caused by radiation therapy (bulky oxidative lesions and DSBs).[10] Hence, it has been proposed that decreased expression of ERCC1-XPF might mediate increased susceptibility to chemoradiation and improved clinical outcome. It is therefore not surprising that *ERCC1* has been extensively evaluated as a biomarker in NSCLC and HNSCC, with over 90 peer-reviewed reports published on the subject.

However, it is important to emphasize that the expression level of ERCC1-XPF has not been established as rate limiting for NER, ICL, or DSB repair, therefore the influence of ERCC1-XPF protein levels on the DNA repair capacity of cells or tumors is not known.

XRCC1 scaffold protein

XRCC1 is an equally promising candidate biomarker involved in the repair of oxidative DNA damage and single-strand breaks (SSBs) (Figure 2), two types of DNA damage abundantly produced by ionizing radiation. XRCC1 does not have enzymatic activity, but it is a critical scaffold protein for base excision repair (BER) and SSB repair (reviewed in Kennedy and D'Andrea,[8] Hoeijmakers,[16] Ladiges,[17] and Almeida and Sobol).[18] XRCC1 interacts strongly with PARP1, which recognizes SSBs, and LIGIII that seals SSBs and BER intermediates.[17,19] Cells lacking XRCC1 are hypersensitive to ionizing radiation, oxidative stress and alkylating agents (reviewed by Caldecott).[19] It is therefore plausible that reduced expression of XRCC1 in cancer patients may lead to increased susceptibility to chemoradiation and improved patient survival. However, like ERCC1-XPF, *XRCC1* has not been established as rate limiting for DNA repair. Thus, the impact of low expression of XRCC1 on a cell's capacity for BER and SSB is not known.

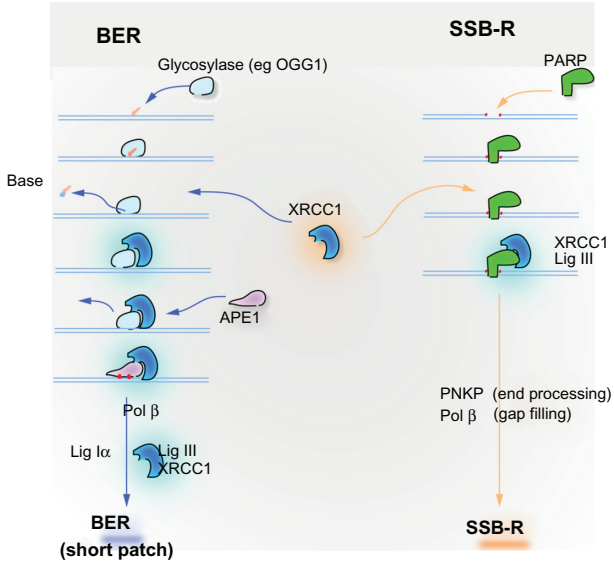

Figure 2 XRCC1 is instrumental in base excision repair (BER) of small oxidative lesions and a related mechanism for the repair of single-strand breaks (SSB-R), both caused by ionizing radiation. Oxidative damage and alkylation leads to small alterations of bases that are principally repaired through BER pathway. Damaged bases are recognized and excised by glycosylases, such as OGG1, which removes the abundant oxidative lesion 8-oxodeoxyguanosine. Excision of the damaged base leaves an abasic (AP) site. The DNA backbone adjacent to the AP site is incised by APE1 endonuclease to create a single-strand break (SSB). XRCC1 has no enzymatic activity, but is critical as a scaffolding protein in BER. It is recruited to the site of damage by the glycosylase or by PARP1, which binds the newly created SSB. XRCC1 forms a tight complex with LIG3, the ligase that seals the SSB repair intermediate to complete BER. Primary SSBs, a common consequence of ionizing radiation, are directly recognized by PARP1, which recruits XRCC1-LIG3 to repair the broken strand. PNKP removes 3′ phosphate groups that block DNA ligation by LIG3. Polβ may be required to replace missing nucleotides at the site of the break.

Methods to assess biomarkers and clinical endpoints

Available methods to interrogate DNA repair

Directly measuring NER, DSB repair, ICL repair, or BER would be the ideal method for predicting an individual's DNA repair capacity. However measuring DNA repair requires viable, and for some pathways, replicating cells. Thus, currently it is not possible to rapidly measure DNA repair in clinical samples because it first requires establishing a cell line from peripheral blood mononuclear cells, dermal fibroblasts, or tumors. Hence measuring DNA repair protein expression is used as a surrogate. Multiple techniques are available to measure ERCC1 and XRCC1 expression including immunohistochemistry or immunofluorescence of fixed tissue sections, quantification of mRNA expression by qRT-PCR, or quantification of protein expression by immunoblot if frozen specimens are available. It must be strongly emphasized, however, that it is not established that ERCC1 is rate limiting for NER or ICL repair, or that XRCC1 is rate limiting for BER or SSB repair. *ERCC1* and *XRCC1* can also be investigated by sequencing DNA to detect functional single nucleotide polymorphisms (SNP) affecting protein function or expression level.

Measuring protein expression

Immunohistochemistry (IHC) and immunofluorescence are semi-quantitative methods that permit estimation of protein expression level in clinical samples. The intensity of the histochemical reaction or fluorescent signal varies with the expression level of the protein of interest and can be scored as positive versus negative or on a graded scale. These methods are advantageous since they employ paraffin embedded tissue specimens, which are readily available. However, several caveats must be considered while interpreting data from immunohistochemical methods. Protein expression within a given tumor may vary from one area to another.[20,21] Therefore expression measured on a biopsy specimen or in a tissue core in an array, which represent only a small fraction of a tumor, may not reflect overall expression. In one patient cohort, however, it was established that ERCC1 expression in biopsies correlated with expression measured in tumor sections.[22] Another important technical consideration is the

fact that tissue collection method, handling, storage, fixation, processing, and analysis influence the biomarker readout, and causes inter-study variability.[23] This has led to the publication of guidelines for evaluation of biomarkers, in an attempt to unify methods of biomarker analysis.[24]

Equally important, immunodetection methods are by definition indirect measures of protein expression, dependent upon the sensitivity and specificity of the antibody used. The specificity of the commercially available antibodies is rarely rigorously tested. ERCC1 protein expression was erroneously quantified in virtually all oncology studies prior to 2010 due to the implementation of an antibody raised against ERCC1 that lacks specificity.[25] Finally, methods for quantifying and scoring biomarker expression vary from study to study, and are somewhat subjective. For instance, biomarker positivity can be defined as the presence of any staining detected by a pathologist, calculated as an H-score based on the staining intensity and number of positive cells, or quantified by an automated system to minimize subjectivity. Thus, while immunohistochemical methods are potentially useful for quantifying biomarker protein expression, multiple factors can introduce intra- or inter-study variability.

Measuring mRNA expression

mRNA expression is often used as a surrogate marker for protein expression. Typically this is done by quantitative RT-PCR, using primers specific for the target biomarker. The advantages of quantifying mRNA are that the method is very sensitive, highly specific, and can be applied to fixed specimens. However, quantitative methods to measure mRNA levels are not readily available outside of biomedical research facilities. Importantly, mRNA and protein expression do not always correlate.[26,27] Translational regulation, post-translational modification and protein stability alter protein levels independently of mRNA.[28] So while mRNA levels can be a useful biomarker to predict clinical outcomes, mRNA levels do not necessarily reflect protein levels. Therefore, changes in mRNA levels should not be used to infer changes in biological activity in the absence of experimental evidence.

Genomic approaches

Base changes in a gene can lead to reduced expression of the encoded protein if they affect the promoter, 5′ or 3′ untranslated sequence, regulatory miRNA binding sites, splice sites, or the coding sequence if the change leads to protein misfolding or destabilization, or utilization of a less abundant tRNA during translation. Missense mutations in the coding sequence can also alter protein function by affecting protein:protein interactions or catalytic activity. Single nucleotide polymorphisms (SNPs) are defined as single base changes that occur in more than 1% of the population. They occur every 360 bases in the human genome, and, thus, affect all genes (reviewed by Kim and Misra).[29] The National Center for Biotechnology Information (www.ncbi.nlm.nih.gov/projects/SNP reports 246 SNPs in *ERCC1*, and 550 SNPs in *XRCC1*. In silico, in vitro, or epidemiological studies can be used to identify SNPs with the highest likelihood of being a useful biomarker. This includes SNPs with a known impact on mRNA level or protein expression, or activity. Fourteen SNPs in *ERCC1* and eleven for *XRCC1* have been investigated in NSCLC and/or HNSCC. The advantages of analyzing SNPs as biomarkers are that multiple SNPs can be evaluated in one sample using an array and DNA hybridization method and require only DNA extracted from a simple blood draw.[29,30] However, it is important to remember that the genotype of a tumor may differ from the germline genotype found in the rest of the body, as tumors are inherently genomically unstable and accumulate DNA mutations. Therefore SNPs identified in a patient's blood sample may not reflect a patient's tumor's genotype.[31] Furthermore, because SNPs are much more abundant than recombination events in the human genome, they are inherited in clusters, referred to as haplotypes. Thus, a SNP in *ERCC1* or *XRCC1* could be a useful biomarker for predicting outcomes in cancer without having any impact on DNA repair.

Clinical endpoints

In oncology, clinical outcomes for which it would be desirable to have biomarkers include: (1) risk of cancer, (2) prognosis in untreated patients, (3) tumor response to therapy, (4) severity of treatment-related toxicities, (5) progression-free survival, and (6) overall survival. DNA repair-related endpoints could logically contribute to any of these endpoints, in particular when genotoxic chemotherapeutics or radiation is the therapy of choice.

One of the most widely recognized risk factors for NSCLC and HNSCC is smoking. The pathogenesis of these tumors involves tobacco-related DNA damage. It is rational to hypothesize that persons with low expression of ERCC1 or XRCC1 may have impaired ability to remove tobacco-induced DNA damage and therefore are more likely to develop smoking-related cancers. The best way to test this hypothesis is with well-powered prospective risk analysis. But these types of studies are difficult to conduct because they necessitate large cohorts and long follow-up times. For instance, >520,000 patients would have to be followed for

10 years to find 116 lung cancer and 82 HNSCC.[32] Thus, most published studies evaluating cancer risk associated with *ERCC1* and *XRCC1* are retrospective case-control studies, which have their inherent limitations.

Since DNA repair-related biomarkers could have value for multiple clinical endpoints, they could potentially have prognostic or predictive value. *Prognostic* biomarkers estimate progression-free or overall survival in an untreated patient population. It gives information on the natural course of the disease.[33] In contrast, *predictive* biomarkers estimate how likely a given treatment is expected to work (efficacy). Predictive value is determined in prospective randomized trial settings with treatment and control arms. Both prognostic and predictive biomarkers are useful but they require different study designs. Once identifying a biomarker of interest, validation is essential and ultimately the greatest barrier to implementation of the biomarker in clinic practice.[34] Validation includes establishing that a biomarker of interest (expression, genotype) consistently predicts a particular clinical outcome (response rate, progression free survival, overall survival). Thus, validation requires multiple clinical studies conducted by multiple independent groups. With these considerations in mind, we now critically review the literature on *ERCC1* and *XRCC1* SNPs as biomarkers in NSCLC and HNSCC.

ERCC1 as biomarker for NSCLC and HNSCC

ERCC1 as a biomarker for cancer risk

Two SNPs, Asn118Asn and C8092A, have been described as potentially affecting *ERCC1* expression. Asn118Asn involves a synonymous polymorphism at codon 118, where AAC is changed to AAT. While the amino acid sequence does not change, the variant (T) allele is associated with lower mRNA and protein levels in ovarian cancer cells.[35,36] C8092 is in the 3′-UTR of *ERCC1*. The 3′-UTR is implicated in translational repression of *ERCC1* mRNA.[28] However the impact of the polymorphism on *ERCC1* protein expression has not been critically evaluated to date. In patients, the C8092A polymorphism correlates neither with mRNA,[37] nor with protein levels.[38] Numerous other SNPs in *ERCC1* have been studied, but like C8092, their functional impact on *ERCC1* expression or activity has not been clearly established.

Studies evaluating *ERCC1* as a potential biomarker to predict the risk of developing NSCLC or HNSCC rest principally on SNP analysis. There are ten studies examining *ERCC1* SNPs in relation to NSCLC.[32,39–47] In these studies, only 14 of 246 reported SNPs in *ERCC1* were evaluated, with just six SNPs analyzed in greater than one study (Table 1). Most report retrospective case-controlled studies focused on Asn118, C8092, and IVS3. While case-control studies are important for identifying new biomarkers, they have inherent biases that can limit the generalization of the results. For instance, if the biomarker is not robust, confounding factors in the cohort may lead to erroneous conclusions. In most of the retrospective studies, SNPs in *ERCC1* were not significantly associated with susceptibility of developing NSCLC.[32,39–42,46–48] However, there was not good concordance between studies.[42–45] To clarify the role of SNPs in *ERCC1* as risk factor for NSCLC, meta-analyses were done. When patients from the diverse studies were combined into large data pools, none of the four SNPs in *ERCC1* meeting study inclusion criteria reached statistical significance as a risk factor for NSCLC.[48–50] Furthermore, mRNA levels in blood samples were not identified as a risk factor for lung cancer.[51] In summary, our review of the literature suggests that neither SNPs in *ERCC1* studied to date by more than one group, nor peripheral mRNA levels, constitute a risk factor for NSCLC.

Head and neck cancers are less common than lung cancer. Hence clinical studies to identify biomarkers that predict the risk of developing HNSCC are less frequent and smaller. We identified six studies evaluating whether polymorphisms in *ERCC1* are a risk factor for HNSCC (Table 1).[32,47,52–55] Only four SNPs were assessed more than once: (Asn118Asn), (C8092A), 119216 C > G, and 4855 C > T. None showed statistically significant association with risk of HNSCC, with the exception of one large case control study in which 4855 C > T appeared to be protective.[54] One small retrospective case-controlled study suggested that low *ERCC1* mRNA in peripheral blood might be a risk factor for HNSCC,[56] but the findings could not be confirmed by others after multivariate analysis.[37] Therefore, we conclude that none of the SNPs in *ERCC1* tested thus far, nor peripheral *ERCC1* mRNA levels are definitive risk factors for HNSCC. However, 4855 C > T deserves close attention in future studies. Further, we cannot exclude the possibility that these or other *ERCC1* SNPs may be useful biomarkers in selected subpopulations for predicting cancer risk.

ERCC1 SNPs as biomarkers for clinical outcome

Polymorphisms in *ERCC1* could affect tumor sensitivity to treatment, and hence influence patient outcomes. Patients with a

Table 1 Association between SNPs in *ERCC1* and cancer risk

Cancer	rs	SNPs	Alternate names	Reference	n (case-control)	Risk[a]
NSCLC	rs11615	Asn118 Asn	C118T; 354 C > T; T19007C; C19007T; 3525 C > T	Zhou et al[39]	1752–1358	0
				Matullo et al[32,#]	116–> 520,000	0
				Yin et al[40]	151–143	0
				Hung et al[41]	4460–5217	0
				Yu et al[42]	988–986	0
				Deng et al[43]	315–315	1
				Zienolddiny et al[44]	343–413	1
	rs3212986	C8092A	14443 C > A	Zhou et al[39]	1752–1358	0; 1 in heavy smokers
				Zienolddiny et al[44]	343–413	0
				Yu et al[42]	988–986	0
				Hung et al[41]	4688–4546	0
	rs3212948	19716 C > G	IVS3 174G > C	Shen et al[46]	122–122	0
				Jones et al[167]	452–790	0
				Zienolddiny et al[44]	343–413	0
				Ma et al[45]	1010–1011	2
	rs3212930	(–)433 T > C		Ma et al[45]	1010–1011	0
				Yu et al[42]	988–986	1
	rs3212961	4855 C > T	IVS5 + 33 C > A; 17677 C > A	Shen et al[46]	122–122	0
				Yu et al[42]	1000–1000	0
				Zienolddiny et al[44]	343–413	0
	rs3212955			Ma et al[45]	1010–1011	0
				Jones et al[167]	452–790	0
	rs3212981			Ma et al[45]	1010–1011	0
	rs16979802	15310 C > G		Zienolddiny et al[44]	343–413	1
	rs3212951			Ma et al[45]	1010–1011	0
	rs1007616			Ma et al[45]	1010–1011	2
	rs1319052			Jones et al[167]	452–790	0
	rs735482			Jones et al[167]	452–790	0
	rs2298881	262 G > T		Yu et al[42]	988–986	0; (1) in smokers
	unnamed			Ma et al[45]	1010–1011	0
HNSCC	rs11615	Asn118 Asn	354 T > C; 19007 T > C; 3525 C > T	Abbasi et al[53]	257–769	0
				Canova et al[54]	1511–1457	0
				Matullo et al[32]	82–> 520,000	0
	rs3212986	C8092A	14443 C > A	Abbasi et al[53]	257–769	0
				Sugimura et al[52]	122–244	(1); 1 in smoker
				Sturgis et al[55]	313–313	(2)
	rs3212948	19716 C > G	IVS3 + 74C > G	Canova et al[54]	1511–1457	0
				Jones et al[167]	175–790	0
	rs3212961	4855 C > T	IVS5 + 33C > A	Abbasi et al[53]	257–769	0
				Canova et al[54]	1511–1457	2
	rs1319052			Jones et al[167]	175–790	0
	rs735482			Jones et al[167]	175–790	0
	rs3212955			Jones et al[167]	175–790	0

Notes: [a]Risk for variable allele, 0 = non significant, (1) = trend to increased, 1 = increased, (2) = trend to protective, 2 = protective; [#]retrospective analysis of prospective study.
Abbreviations: HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancers; rs, reference SNP; SNPs, single nucleotide polymorphisms.

polymorphic variant of *ERCC1,* which results in impaired NER and/or ICL repair capacity, may be exquisitely sensitive to chemotherapy with genotoxic agents or radiation. This could mean their tumors respond better to chemoradiation therapy and outcomes are improved. Alternatively, the host may be hypersensitive to genotoxic stress leading to exaggerated side effects of therapy and poor outcomes.

In NSCLC, we identified sixteen studies testing whether *ERCC1* polymorphisms influence clinical outcome,[38,57–71] including five prospective studies (Table 2).[58,62,69,70] The only two SNPs tested were Asn118 and C8092. The results are inconsistent, weakening the generalizability of the conclusions. When more than 500 patients from multiple studies were pooled into a single meta-analysis, Asn118 Asn

Table 2 Association between SNPs in *ERCC1* and clinical outcome

Cancer	rs	SNPs	Alternate names	Reference	n	Outcome[a]
NSCLC	rs11615	Asn118 Asn	C118T; 354 T > C; 19007 T > C; 3525 C > T	Zhou et al[63]	128	0
				Gandara et al (2005)[b]	526	0
				Suk et al[59]	214	0 (toxicity)
				De Las Penas et al[71,b]	135	0
				Tibaldi et al[61]	65	0
				Takenaka et al[73]	122	0
				Vinolas et al[62,b]	94	0
				Park et al[64]	178	(1); 1 for stage III
				Ryu et al[65]	109	1
				Isla et al[68]	62	1
				Su et al[66]	230	1
				Kalikaki et al[57]	119	1
				Okuda et al[38]	90	1
				Yin et al[67]	257	1
				Li et al[70,b]	115	2
				Zhou et al[69,b]	130	2
	rs3212986	C8092A	14443 C > A	Zhou et al[63]	128	1
				Suk et al[59]	214	1 (toxicity)
				Park et al[64]	178	0
				Okuda et al[38]	90	1
				Takenaka et al[73]	122	1
				Kalikaki et al[57]	119	2
				Li et al[70,b]	115	2
HNSCC	rs3212986	C8092A	14443 C > A	Quintela-Fandino et al[74]	103	–1
	rs735482	Lys259Thr	1264 A > C	Grau et al[75,b]	47	0
				Carles et al[76]	108	1 (but only 4% of carrier)

Notes: [a]Outcome for variable allele, 0 = non significant, (1) = trend to worse, 1 = worse, (2) = trend to better, 2 = better; [b]prospective study.
Abbreviations: HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancers; rs, reference SNP; SNPs, single nucleotide polymorphisms.

was predictive of tumor response to chemotherapy.[72] As expected, the variant allele (C→T), which presumably causes lower *ERCC1* expression, correlated with a higher response rate.[72] However, this meta-analysis excluded one important report, a large phase Phase III study (n = 526) in which Asn118 did not predict clinical outcome, including response to treatment.[58] These conflicting results, derived from equally large studies, suggest that this *ERCC1* SNP is not a robust predictive biomarker in an unselected population. To our knowledge, C8092 has not been evaluated in a large prospective study or in a meta-analysis as a predictor of clinical outcomes in NSCLC. In retrospective cohorts, C8092 showed mixed results as predictive biomarker. The general tendency was slightly weighed toward the variant allele (C→A) predicting worse outcomes.[38,59,63,73] In summary, none of the SNPs in *ERCC1* tested have been identified as strongly predictive biomarkers for outcomes in NSCLC, but C8092 emerges as a potentially promising candidate.

In HNSCC, we identified only three studies evaluating the predictive value of SNPs in *ERCC1* (Table 2).[74–76] Like NSCLC, in HNSCC, there was a trend towards an association between the variant allele of C8092 (C→A) with poor response to chemoradiation, and no correlation with survival.[74] A new SNP (rs735482) located in the 3′UTR of *ERCC1* was evaluated for predictive value of clinical outcome in two separate cohorts, but results were mixed.[75,76] Therefore, we conclude that there is currently no strong evidence that SNPs in *ERCC1* can predict clinical outcome in HNSCC.

ERCC1 protein expression as a biomarker of patient outcomes in NSCLC

While SNPs are often used as a crude estimate of ERCC1 expression or activity, immunodetection approaches permit a more direct quantification of ERCC1 protein level in tumor samples. We identified 17 studies addressing whether quantification of ERCC1 expression in NSCLC tumors by immunohistochemistry has prognostic or predictive value (Table 3).[27,38,60,73,77–91] In a seminal retrospective analysis of a phase III trial, more than 780 patients with fully resected early stage NSCLC were randomized to observation versus

Table 3 Association between ERCC1 protein expression and clinical outcome

Cancer	Reference	n	Outcome[a]
NSCLC	Planchard et al[90]	188	0
	Koh et al[89]	130	0
	Zheng et al[27]	187	1
	Kang et al[88]	82	1
	Okuda et al[38]	55	(2)
	Okuda et al[91]	90	2
	Olaussen et al[81]	783	2
	Azuma et al[84]	67	2
	Fujii et al[83]	35	2
	Lee et al[87]	130	2
	Holm et al[86]	163	2; men $P = 0.005$, women $P = 0.7$
	Azuma et al[85]	34	2
	Lee et al[82]	50	2
	Ota et al[80]	156	2
	Reynolds et al[79,b]	69	2
	Vilmar et al[78,b]	264	2
	Wang et al[77]	214	2
	Taillade et al[22]	34	Biopsy vs tumor correlation
	Gomez-Roca et al (2009)	49	Primary vs metastasis
	Kang et al[164]	82	Primary vs metastasis
	Papay et al (2009)	17	Change after chemotherapy
	Besse et al (2010)[c]	761	Brain metastasis
HNSCC	Fountzilas et al[31]	37	0
	Koh et al[89]	80	0
	Handra-Luca et al[97]	96	2
	Jun et al[98]	45	2
	Fountzilas et al[31,b]	26	2

Notes: [a]Outcome for low ERCC1 expression, 0 = non significant changes, (1) = trend to worse, 1 = worse, (2) = trend to better, 2 = better; [b]prospective study; [c]retrospective analysis of prospective study.
Abbreviations: HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancers.

multidrug chemotherapy.[81] The results suggested that tumoral ERCC1 protein expression was a biomarker with a complex profile. High ERCC1 levels correlated with good prognosis for untreated cases. But patients with low ERCC1 levels did significantly better when treated with multidrug chemotherapy. These results are consistent with the prediction that decreased expression of ERCC1 could promote sensitivity to genotoxic chemotherapy. Most studies agree that low ERCC1 protein expression is a marker for better clinical outcome after genotoxic therapy in NSCLC. Thirteen of 17 studies reported that low ERCC1 correlated with better clinical outcome (total n = 1815),[77–85,87,91,92] or had a statistical trend towards better outcome (total n = 218).[38] Two studies showed no correlation between ERCC1 level and outcome (n = 218),[89,90] while two studies showed a significantly worse outcome (total n = 269)[27,88] in patients with tumors expressing low levels of ERCC1. A recent meta-analysis evaluated NSCLC patients treated with platinum compounds.[93] Low expression of ERCC1 in tumors quantified by immunohistochemistry was associated with a better clinical response to cisplatin, which translated into better survival.[93] Despite some variability between individual studies, ERCC1 appears to emerge as a good candidate biomarker predictive of clinical outcome in NSCLC. An important point, however, is that in all 18 of the studies the monoclonal antibody, 8F1 was used to measure ERCC1 expression, and this antibody is not specific for ERCC1.[25] Therefore, the claim that low ERCC1 expression correlates with better outcome is inaccurate. The more precise conclusion is that low 8F1 signal correlates with better outcome. More recent studies comparing 8F1 and another antibody specific for ERCC1 reveal that they have different predictive capacities with relation to clinical outcomes in cervical cancer.[94]

In HNSCC, only five studies (total n = 285) evaluated whether ERCC1 protein expression in tumors correlated with clinical outcome (Table 3).[31,95–98] The 8F1 antibody was used in all of the studies. Low 8F1 signal was associated with better outcome in three studies (total n = 168),[95,97,98] while no significant association was found in the other two (n = 117).[31,96]

ERCC1 transcript levels as a biomarker in NSCLC and HNSCC

As a surrogate marker of *ERCC1* expression, *ERCC1* mRNA was measured in NSCLCs in cell lines,[99] and in six retrospective[68,100–104] and six prospective studies.[105–110] The results were mixed, but most studies showed an association between low *ERCC1* mRNA and better clinical outcome, either significantly (seven studies)[100,102–105,108,109] or with a statistical trend (three studies).[68,105,110] In a meta-analysis, both low tumoral mRNA and protein levels correlated with a better response rate to chemoradiation and overall patient survival.[93] While assays used to measure mRNA levels in tumors are not yet readily available for clinical use in all cancer centers, *ERCC1* mRNA may prove to be a reasonable predictive biomarker of outcome in NSCLC patients treated with platinum-based chemotherapy.[93] Interestingly, *ERCC1* mRNA and protein levels were found to be not correlated in NSCLC[27] and inversely correlated in ovarian cancer.[111] Furthermore, mRNA levels were not correlated with chemosensitivity in NSCLC cell lines[99] nor with response to chemotherapy in HNSCC.[31] Thus, the relationship between *ERCC1* mRNA and DNA repair capacity is not direct and remains to be clarified.

XRCC1 as biomarker for NSCLC and HNSCC

XRCC1 as a biomarker for cancer risk

Similar studies have sought to establish whether *XRCC1* is linked with cancer risk, prognosis, or treatment outcome. SNPs in *XRCC1* have been extensively studied in NSCLC, although only 9 SNPs out of 550 possible have been evaluated in published reports. The majority of trials focus on Arg194Trp, Arg280His, and Arg399Gln, three nonsynonymous SNPs in *XRCC1* (reviewed by Schneider et al).[112] Four studies, including two large ones, also analyzed a SNP in the *XRCC1* promoter (−77T→C).[113–116] The variant allele −77T→C alters a binding site for the zinc finger transcription factor SP1, leading to reduced transcription of *XRCC1*.[113] The variant allele at position 399 (Gln) correlates with lower DNA repair capacity and increased genomic instability in multiple studies.[117–121] These functional SNPs in *XRCC1* are attractive candidate biomarkers in cancer.

XRCC1 SNPs as biomarkers for cancer risk

The assessment of SNPs in *XRCC1* as risk factors for developing NSCLC has focused mainly on *XRCC1* Arg194Trp, Arg280His and Arg399Gln, and to a lesser degree on −77T→C (Table 4).[32,41,44,67,112–116,122–143] Studies failed to identify significant association between Arg194Trp, Arg280His, and Arg399Gln genotypes and NSCLC risk. However, −77T→C did emerge as a significant risk factor in two large studies.[113,114] This is consistent with the notion that low *XRCC1* expression leads to impaired BER and SSB repair, greater mutational load and therefore increased cancer risk. A well conducted meta-analysis pooling more than 10,000 patients for the analysis of Arg194Trp, Arg280His, and Arg399Gln, and more than 1,000 patients for the analysis of Pro206Pro and −77T→C found that, in NSCLC, −77T→C was associated with cancer risk ($P < 0.0001$), while none of the other four SNPs analyzed in *XRCC1* showed association.[50] Furthermore, this meta-analysis reviewed a total of 241 associations in 16 genes, and *XRCC1* −77T→C was one of the only two associations that maintained a significant association through the most stringent analysis. Thus, there is strong epidemiological and biological credibility supporting *XRCC1*–77T→C as a risk factor for NSCLC.

In HNSCC, only five SNPs have been evaluated as cancer risk factors.[32,54,144–154] Four of them have been evaluated more than once: Arg194Trp, Arg280His, Arg399Gln, and Pro206Pro (Table 4). The results were mixed for all four SNPs, but primarily showed no significant association with cancer risk, except for a tendency for the homozygous variant 399Gln-Gln to be protective in Caucasians in one large pooled study.[154] Interestingly, when patients from individual studies were pooled for a meta-analysis, Arg194Trp emerged as a significant risk factor for HNSCC, as well as for other solid cancers (skin, esophageal, and stomach).[50] It will be interesting to follow whether future studies can validate this SNP as a biomarker for risk stratification in HNSCC.

XRCC1 SNPs as biomarkers for clinical outcome

Biologically, genetic polymorphisms in *XRCC1* could potentially predict clinical outcome, because reduced *XRCC1* expression in animal models confers sensitivity to ionizing radiation. We identified eleven studies[57,67,71,115,155–161] looking at *XRCC1* SNPs (Arg194Trp, Arg280His, Arg399Gln, and −77T→C) including five prospective studies,[71,155,157,159,160] totaling more than 1700 patients (Table 5). Results were mixed for Arg194Trp: three studies showed no association (total n = 382),[155–157] one showed a worse prognosis for the allelic variant (n = 229),[158] and one showed a better prognosis (n = 82).[159] Results for Arg399Gln were also mixed, with significantly worse overall survival or toxicity for the allelic variant in three studies (total n = 515),[57,67,156] while a better prognosis was found in two studies (n = 238)[71,160] and no association was found in other studies (total n = 559).[155,157–159,161] Finally, Arg280His showed no significant association with any outcome (2 studies; total n = 428). A meta-analysis and additional studies to examine −77T→C are needed to determine if SNPs in *XRCC1* have any value for predicting clinical outcomes in patients with NSCLC treated with chemoradiation.

In HNSCC, *XRCC1* has not been extensively studied. We identified only four reports assessing the predictive value of SNPs in *XRCC1*, focusing predominantly on Arg399Gln,[74,76,145,162] and to a lesser extent Arg194Trp[145,162] (Table 5). Results for Arg399Gln were mixed; two out of the four studies (total n = 293) showed a better outcome for the allelic variant.[74,162] Interestingly, Arg194Trp, which was previously identified as a significant risk factor for HNSCC, did not influence treatment outcome.[162] As with NSCLC, more studies and larger prospective studies are needed to evaluate whether SNPs in *XRCC1* influence response to treatment in HNSCC.

Table 4 Association between SNPs in *XRCC1* and cancer risk

Cancer	rs	SNPs	Alternate names	Reference	n (case-control)	Risk[a]
NSCLC	rs1799782	Arg194Trp	194 C > T; 194 R > W; 194 Arg > Trp; C26304T	Butkiewicz et al[124]	96–96	0
				Hu et al[114]	710–710	0
				Shen et al[46]	122–122	0
				Matullo et al[32]	116–> 520,000	0
				Hao et al[113]	1024–1118	0
				Zienolddiny et al[44]	343–413	0
				Yin et al[131]	247–253	0
				Hung et al[41,b]	6463–6603	0
				Improta et al[126]	940–121	0
				Tanaka et al[130]	50–50	0
				Ratnasinghe et al[128]	108	0; 2 in drinkers
				David-Beabes[132]	332–704	0; 2 in African-Americans
				Schneider et al[112]	446–622	0; 2 in heavy smokers
				Hung et al[127,b]	2188–2198	0; 2 in heavy smokers
				Chen et al[56]	109–109	(1)
				Pachouri et al[133]	103–122	(1)
				De Ruyck et al[116]	110–110	2
				Yin et al[67]	55–74	2
	rs25489	Arg280His	280 G > A; 280 R > H; 280 Arg > His	Butkiewicz et al[124]	96–96	0
				Misra et al[122,b]	305–305	0
				Vogel et al[124]	265–272	0
				Schneider et al[112]	446–622	0
				Shen et al[46]	122–122	0
				Hao et al[113]	1024–1118	0
				Zienolddiny et al[44]	343–413	0
				Hung et al[41]	6463–6603	0
				Yin et al[67]	55–74	0
				Yin et al[131]	247–253	0; 2 in non-smokers
				Hung et al[127,b]	2188–2198	0; 2 in heavy smokers
				Ratnasinghe et al[128]	108	1
				De Ruyck et al[116]	110–110	2
	rs25487	Arg399Gln	G28152A; 399 G > A; 399 R > Q; 399 Arg > Gln	Butkiewicz et al[124]	96–96	0
				David-Beabes[132]	332–704	0
				Ratnasinghe et al[128]	108	0
				Chen et al[56]	109–109	0
				Ito et al[135]	178–449	0
				Popanda et al[137]	463–460	0
				Vogel et al[134]	265–272	0
				Zhang et al[139]	1000–1000	0
				Hu et al[114]	710–710	0
				Hung et al[127,b]	2188–2198	0
				Zienolddiny et al[44]	343–413	0
				Hao et al[113]	1024–1118	0
				Yin et al[131]	247–253	0
				Lopez-Cima et al[136]	516–533	0
				Hung et al[41,b]	6463–6603	0
				Improta et al[126]	940–121	0
				Yin et al[67]	55–74	0
				De Ruyck et al[116]	110–110	0; 1 in light smokers, 2; in heavy smokers

(*Continued*)

Table 4 (*Continued*)

Cancer	rs	SNPs	Alternate names	Reference	n (case-control)	Risk[a]
				Misra et al[122,b]	305–305	0; (2) in heavy smokers
				Schneider et al[112]	446–622	0; 2 in heavy smokers
				Ryk et al[138]	177–153	0; 2 in non-smokers
				Park et al[140,b]	192–135	(1) for SCC
				Zhou et al[141]	1091–1240	(1)
				Sreeja et al[142]	171–211	1
				Divine et al[143]	172–143	1 in Caucasian but not Hispanic
				Shen et al[46]	122–122	(2)
				Matullo et al[32]	116–> 520,000	2 (by stepwise regression)
				Pachouri et al[133]	103–122	2
	rs3213245	–(77) T > C		De Ruyck et al[116]	110–110	0
				Hsieh et al[115]	294–288	0
				Hao et al[113]	1024–1118	1
				Hu et al[114]	710–710	1
	rs915927	Pro206Pro	206 A > G; 206 pro = pro	Matullo et al[32]	116–> 520,000	0
				Yin et al[131]	247–253	1
				Yin et al[67]	55–74	1
	rs17852150	Gln632Gln	632 G > A; 632 Gln = Gln	Yin et al[131]	247–253	0
				Yin et al[67]	55–74	0
	rs2307191	Pro161Leu	161 Pro > Leu	Tanaka et al[130]	50	0
	rs2307177	Tyr576Ser	576 Tyr > Ser	Tanaka et al[130]	50	0
	n/a	Arg59Cys		Zienolddiny et al[44]	343–413	ND
HNSCC	rs1799782	Arg194Trp	194 C > T; 194 R > W; 194 Arg > Trp; C26304T	Sturgis et al[151]	203–424	0; 2 for oral and pharyngeal cancer
				Olshan et al[148]	182–202	0
				Varzim et al[168]	88–178	0
				Matullo et al[32]	82–> 520,000	0
				Harth et al[146]	312–300	0
				Applebaum et al[144]	722–815	0
				Csejtei et al[145]	108–102	0
				Kowalski et al[149]	92–124	(1)
				Tae et al[150]	147–168	1
	rs25489	Arg280His	280 G > A; 280 R > H; 280 Arg > His	Tae et al[150]	147–168	0
				Harth et al[146]	312–300	0
				Applebaum et al[144]	722–815	0
				Sturgis et al[151]	203–424	0
				Cho et al[152]	334–283	2
	rs25487	Arg399Gln	G28152A; 399 G > A; 399 R > Q; 399 Arg > Gln	Varzim et al[168]	88–178	0
				Cho et al[152]	334–283	0
				Tae et al[150]	147–168	0
				Huang et al[154]	555–792	0; 2 in Caucasian
				Harth et al[146]	312–300	0
				Canova et al[54]	1478–1424	0
				Applebaum et al[144]	722–815	0; (1) in p16 neg smokers

(*Continued*)

Table 4 (*Continued*)

Cancer	rs	SNPs	Alternate names	Reference	n (case-control)	Risk[a]
				Csejtei et al[145]	108–102	0
				Kowalski et al[149]	92–124	0
				Sturgis et al[151]	203–424	(1)
				Olshan et al[148]	182–202	2
				Gal et al[153]	279	2; for overall survival only
	rs915927	Pro206Pro		Matullo et al[32]	82–> 520,000	0
				Canova et al[54]	1495–1436	0
	rs762507			Canova et al[54]	1447–1397	0

Notes: [a]Risk for variable allele, 0 = non significant, (1) = trend to increased, 1 = increased, (2) = trend to protective, 2 = protective; ND = not done; [b]retrospective analysis of prospective study.
Abbreviations: HNSCC, head and neck squamous cell carcinoma; NSCLC, non-small cell lung cancers; rs, reference SNP; SCC, squamous cell carcinoma; SNPs, single nucleotide polymorphisms.

XRCC1 expression as a biomarker of patient outcomes in cancer

There is very little data on XRCC1 expression in tumors, despite the fact that at least in NSCLC cell lines increased *XRCC1* mRNA is significantly associated with cisplatin resistance.[163] There are two studies (both using the same patient cohort) reporting XRCC1 expression in NSCLC, as measured by immunohistochemistry.[88,164] XRCC1 protein expression did not correlate with either response to treatment or survival. Interestingly, more than half of the metastases had a stronger immunohistochemical signal than their matched primary tumor, suggesting that the level of XRCC1 may increase during cancer progression. This could have therapeutic implications if elevated expression of XRCC1 renders cells more resistant to treatment.

Only one study evaluated XRCC1 protein expression and clinical outcome in HNSCC.[165] High XRCC1 expression was correlated with resistance to radiotherapy. There is also a

Table 5 Association between SNPs in *XRCC1* and clinical outcome

Cancer	rs	SNPs	Alternate names	Reference	n	Outcome[a]
NSCLC	rs1799782	Arg194Trp	194 C > T; 194 R > W; 194 Arg > Trp; C26304T	Petty et al[155,b]	49	0
				Wang et al[156]	139	0
				Yuan et al[157,b]	199	0
				Yoon et al[158]	229	1
				Sun et al[159,b]	82	2
	rs25489	Arg280His	280 G > A; 280 R > H; 280 Arg > His	Yoon et al[158]	229	0
				Yuan et al[157,b]	199	(2)
	rs25487	Arg399Gln	G28152 A; 399 G > A; 399 R > Q; 399 Arg > Gln	Yoon et al[158]	229	0
				Petty et al[155,b]	49	0
				Sun et al[159,b]	82	0
				Yuan et al[157]	199	0
				Gurubhagavatula et al[161,c]	103	(1)
				Kalikaki et al[57]	119	1
				Yin et al[67]	257	1
				Wang et al[156]	139	1 (toxicity)
				Giachino et al[160,b]	203	2 (toxicity)
				De las Penas et al[71,b]	135	2
	rs3213245	–(77) T > C		Hsieh et al[115]	294	0
	rs1799782	Arg194Trp	194 C > T; 194 R > W; C26304T	Geisler et al[162]	190	0
				Csejtei et al[145]	108	1
	rs25487	Arg399Gln	G28152A; 399 G > A; 399 R > Q	Carles et al[76]	108	0
				Csejtei et al[145]	108	0
				Geisler et al[162]	190	2
				Quintela-Fandino et al[74]	103	2

Notes: [a]Outcome for variable allele, 0 = non significant, (1) = trend to worse, 1 = worse, (2) = trend to better, 2 = better; [b]prospective study; [c]retrospective analysis of prospective study.
Abbreviations: NSCLC, non-small cell lung cancers; rs, reference SNP; SNPs, single nucleotide polymorphisms.

paucity of studies on the predictive value of either peripheral or tumor *XRCC1* mRNA in cancer. In contrast to the protein data, *XRCC1* mRNA appears to be lower in early stage lung cancer compared with more advanced cancer.[166]

Conclusion

In summary, for the past decade the biomedical community has evaluated DNA repair genes as potential biomarkers to predict cancer risk and prognosis of cancer patients treated with genotoxic agents. There has been considerable investment toward this endeavor, yet none of the candidate biomarkers, other than *BRCA1* and *BRCA2*, have yet to be translated to clinic use. *ERCC1* and *XRCC1* are two good candidate biomarkers, with robust experimental evidence demonstrating that reduced expression or activity of either protein results in increased genomic instability and sensitivity to DNA damaging agents.[7,9–11,19] To date, investigations as to whether *ERCC1* and *XRCC1* alter cancer risk or outcomes are primarily modest-sized retrospective case controlled studies, which have yielded conflicting results. The strongest associations to date are that a CC genotype at SNP −77 of *XRCC1*, which causes reduced *XRCC1* mRNA, predicts increased risk of NSCLC. For *ERCC1*, there are numerous studies indicating that low mRNA or protein expression is associated with a better prognosis in HNSCC and NSCLC, respectively. However, it is not established that *ERCC1* expression is regulated at the transcriptional level. Furthermore, in the studies measuring protein level, a nonspecific antibody was used. Therefore these studies, while validating the utility of these biomarkers (*ERCC1* mRNA levels or 8F1 immunohistochemical signal) for predicting clinical outcomes, do not directly demonstrate that DNA repair levels are altered in tumors.

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Disclosure

The authors report no conflicts of interest in relation to this paper.

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