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REVIEW ARTICLE

Single nucleotide polymorphisms in DNA repair genes and putative cancer risk

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Abstract Single nucleotide polymorphisms (SNPs) are the most frequent type of genetic alterations between individuals. An SNP located within the coding sequence of a gene may lead to an amino acid substitution and in turn might alter protein function. Such a change in protein sequence could be functionally relevant and therefore might be associated with susceptibility to human diseases, such as cancer. DNA repair mechanisms are known to play an important role in cancer development, as shown in various human cancer syndromes, which arise due to mutations in DNA repair genes. This leads to the question whether subtle genetic changes such as SNPs in DNA repair genes may contribute to cancer susceptibility. In numerous epidemiological studies, efforts have been made to associate specific SNPs in DNA repair genes with altered DNA repair and cancer. The present review describes some of the common and most extensively studied SNPs in DNA repair genes and discusses whether they are functionally relevant and subsequently increase the likelihood that cancer will develop.

Keywords Single nucleotide polymorphism · DNA repair mechanisms · Repair genes · Cancer susceptibility · Cancer treatment

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Introduction

Cancer is a disease resulting from DNA damage caused by endogenous sources or by environmental agents. To counteract the mutagenic effects of DNA lesions, distinct pathways of DNA repair have been evolved (Friedberg et al. 2005). As DNA repair plays a critical role in protecting the human genome from mutagenic lesions, alterations in the DNA repair capacity can give rise to the development of cancer. A number of human disorders, which are characterized by a predisposition to cancer, are caused by defects in single DNA repair genes and therefore a deficiency to remove specific DNA lesions (for review see (Cleaver 2005; Hoeijmakers 2009; Köberle et al. 2005). In addition to these mutational changes, which result in human disorders, many sequence variations between individuals have been observed in human DNA repair genes (Mohrenweiser et al. 2002). Sequence variations at single nucleotides are called single nucleotide polymorphisms (SNPs). They represent the most frequent type of genetic variation between individuals. SNPs are observed with a frequency highly variable between 1 % up to 50 % in the general population. Up-to-date information about SNPs in human DNA repair genes can be found at: http://egp.gs.washington.edu, http://www.ncbi.nlm.nih.gov/SNP/ or http://snp500cancer.nci.nih.gov.

A significant number of SNPs has been identified in sequences of DNA repair genes, which do not code for a protein; the functional significance of most of these SNPs, however, has not been elucidated to date. Of those SNPs within coding sequences, some might have no effect on the protein sequence (synonymous SNPs), while others will lead to substitutions of one amino acid with another (non-synonymous SNPs). There are algorithms available to predict the impact of an amino acid substitution on protein

structure and function. The sorting intolerant from tolerant program (SIFT) uses sequence alignments and is based on the assumption that an evolutionary conserved position within a protein will be intolerant to most changes while a poorly conserved position will tolerate most changes (Ng and Henikoff 2002). The Polymorphism Phenotyping program (PolyPhen) uses structural information and predicts an amino acid substitution as benign, possibly damaging or probably damaging depending on its location within the protein structure (Ramensky et al. 2002). It is estimated that up to 30 % of the repair gene SNPs might impact protein activity (Xi et al. 2004).

It is conceivable that non-synonymous SNPs may be functionally relevant by altering protein function, which could cause differences in the cellular repair capacity and hence influence the susceptibility to cancer. In addition, SNPs in DNA repair genes might also be relevant for the cure of cancer, as DNA damage induced by chemotherapeutic drugs is subjected to repair by the cellular repair machinery (Zamble and Lippard 1995). Cancer cells deficient for DNA repair have been shown to be exquisitely sensitive to chemotherapeutic treatment (Köberle et al. 1997; Usanova et al. 2010). In a vast number of publications, it has been investigated whether SNPs in different DNA repair genes are associated with cancer incidence or therapy success. In this review we will describe some of the common DNA repair gene polymorphisms, discuss their functional significance, and assess their relevance for cancer risk or treatment success.

SNPs in base excision repair genes

Base excision repair (BER) deals with small chemical base alterations, which are formed mostly endogenously due to the cellular metabolism, but can also be induced by chemicals such as alkylating agents. BER removes damaged bases by employing specific glycosylases, which recognize and remove the damaged base leading to an abasic site, which in turn is incised by an apurinic/apyrimidinic endonuclease such as APE1. The remaining sugar fragment will be removed by a phosphodiesterase or lyase, followed by either a short patch excision repair event replacing one nucleotide or by long patch repair, which replaces 2–13 nucleotides. The remaining nick is sealed by a DNA ligase to complete the repair event (Almeida and Sobol 2007; Kim and Wilson 2012; Krokan and Bjoras 2013; Lindahl and Wood 1999; Wallace 2014) (Fig. 1).

SNPs in OGG1

OGG1 is a glycosylase, which excises the common DNA base modification 8-hydroxyguanine (8-oxoG) from DNA (Lindahl 2000). 8-oxoG, the most prominent form of DNA damage induced by exposure to reactive oxygen species (ROS), is highly mutagenic and therefore a possible cause for carcinogenesis. A reduced ability to repair this lesion may therefore lead to an accumulation of mutations and hence cancer.

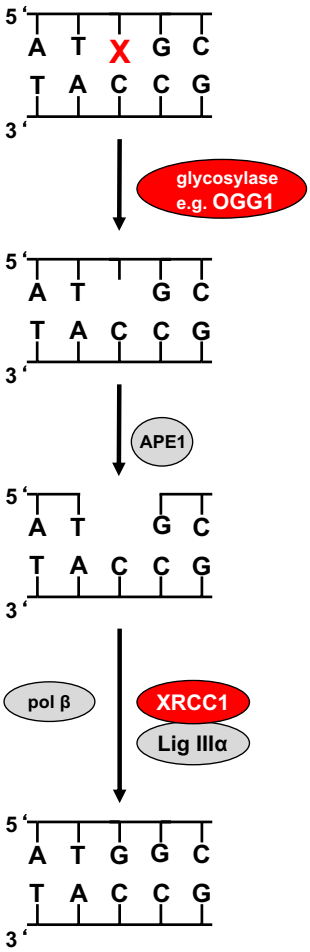

Fig. 1 Base excision repair (BER). Specialized gylcosylases recognize and excise the damaged base (x) leading to an abasic site, which is removed by the action of an AP endonuclease such as APE1 endonuclease, followed by removal of the remaining sugar fragment by a lyase or phosphodiesterase. The resulting gap is filled by the action of DNA pol β, followed by sealing of the remaining nick by the XRCC1-ligase IIIα complex. For a more detailed model refer to (Almeida and Sobol 2007; Kim and Wilson 2012). In *red*: proteins encoded by *OGG1* and *XRCC1* for which common SNPs are described in the text

Four SNPs that lead to a change of amino acids have been described within the coding region of *OGG1* at amino acid coding position 229, 288, 322 and 326. Of these, only Ser326Cys is a common polymorphism, with the 326Cys allele found in 32 % of individuals (Table 1). A number of studies have investigated a possible association between the 326Cys allele and cancer risk, however, with inconsistent data. For squamous cell carcinoma of the esophagus, a

Table 1 Common single nucleotide polymorphisms (SNPs) in genes involved in base excision repair

	SNP	Allele position	Residue	Variant	Frequency	Predictive analyses		SNP reference
						PolyPhen	SIFT	
OGG1	C>G	9184	Ser326	Cys	0.32	Benign	Intolerant	rs1052133
XRCC1	C>T	24,049	Arg194	Trp	0.12	Possibly damaging	Intolerant	rs1799782
	G>A	25,211	Arg280	His	0.10	Benign	Intolerant	rs25489
	G>A	25,897	Arg399	Gln	0.23	Benign	Tolerant	rs25487
	−77T>C	1915[a]			0.22			rs3213245
ADPRT	T>C	40676	Val762	Ala	0.19	Benign	Unknown	rs1136410

[a] SNP located in the 5′ untranslated region (5′UTR) of the *XRCC1* gene

positive association between the 326Cys allele and cancer has been observed suggesting that the variant allele might play a role in carcinogenesis (Xing et al. 2001). In contrast, investigations with prostate cancer suggested a protective effect of the variant allele (Xu et al. 2002). Lung cancer studies have yielded mixed results. The variant allele has been associated with either no effect for lung carcinogenesis (Kohno et al. 1998; Wikman et al. 2000) or was considered a risk factor for lung cancer, especially for squamous cell carcinoma of the lung (Duan et al. 2012; Janik et al. 2011; Le Marchand et al. 2002; Sugimura et al. 1999).

It is also not known whether the amino acid change at residue 326 has any functional significance for BER. Based on in vitro data and observations in lymphocytes and tissue lysates, it has been suggested that the Ser326Cys substitution reduces the incision activity of the OGG1 protein (Janik et al. 2011; Kohno et al. 1998; Smart et al. 2006). However, other studies reported that the variant allele of *OGG1* was not associated with altered OGG1 repair activity (Dherin et al. 1999; Janssen et al. 2001). By using an oligonucleotide containing a single 8-oxoG lesion (Hamann et al. 2009) we assessed the repair activity of OGG1 Ser326 and the 326Cys variant allele. We found no difference in OGG1 repair activity when we compared protein extracts of HeLa cells expressing either Ser326 or 326Cys, indicating that the SNP has no significance for the repair activity of OGG1 (Bettina M. Fischer, unpublished observations). Furthermore, no difference in cellular sensitivity was observed when we treated HeLa cells representing the different 326 alleles with the ROS producing compound menadione (Beate Köberle, unpublished observations). Altogether, based on the conflicting epidemiological data and observations concerning the functional impact, the question still remains whether the *OGG1* Ser326Cys SNP is relevant to cancer risk.

SNPs in XRCC1

XRCC1 has been found to interact with numerous other BER proteins acting as a scaffolding protein (Mutamba et al. 2011; Vidal et al. 2001). Eight SNPs, which will lead to a change in amino acids, have been identified in the coding region of the *XRCC1* gene, with variants Arg194Trp, Arg280His, and Arg399Gln occurring with frequencies of 10 % or more (Table 1).

SNP Arg194Trp and a possible association with lung cancer has been investigated in different studies, the results, however, are quite variable. The 194Trp allele was associated with a protective effect against lung cancer (De Ruyck et al. 2007; Yin et al. 2009), but this observation was not confirmed in other studies (Hao et al. 2006; Hung et al. 2005). Mixed results were also obtained for other cancer entities. While a protective effect of the *XRCC1* variant has been reported for nasopharyngeal carcinoma (Cao et al. 2006) and squamous cell carcinoma (Kang et al. 2007), an increased risk was observed for salivary gland carcinoma (Ho et al. 2007). For alleles 280 and 399, no significant association between the variant form and risk of cancers including lung cancer (Hao et al. 2006; Hung et al. 2005; Yin et al. 2009), salivary gland carcinoma (Ho et al. 2007) and nasopharyngeal carcinoma (Cao et al. 2006) is reported, suggesting that the *XRCC1* SNPs at position 280 and 399 do not play a major role for cancer risk. On the other hand, an increased cancer risk for the variant form of allele 399 was reported for squamous cell carcinoma (Kang et al. 2007) and lung cancer (De Ruyck et al. 2007; Wang et al. 2015).

Whether the described *XRCC1* SNPs are functionally significant is not yet known. SIFT and PolyPhen analyses predict *XPCC1* SNP Arg194Trp to be possibly damaging/intolerant, Arg280His to be benign/intolerant and Arg399Gln to be benign/tolerated (Table 1). Investigations for a possible relationship between DNA damage and *XRCC1* SNPs revealed that the variant allele of Arg399Gln was associated with higher levels of DNA damage, leading to the suggestion that this SNP alters the XRCC1 protein sequence resulting in reduced DNA repair function (Lunn et al. 1999). However, to date no functional assay was used to assess base excision repair activity in relation to the variant allele of Arg399Gln.

In addition to the SNPs, which have been identified in the coding region of *XRCC1* and which lead to amino acid changes, a SNP has been identified, which is located in the 5′ noncoding promoter region of the gene (Table 1) (Hao et al. 2004). The −77 T>C SNP occurs commonly enough for epidemiological studies, with a frequency of 78 % for the T allele and 22 % for the C allele. −77 T>C has been investigated for a possible link with cancer risk, and the results, however, were once again quite variable. De Ruyck et al. (2007) observed no association of the −77 C allele with carcinoma of the lung. However, Hao et al. (2004, 2006) reported that the −77 C allele increased the risk for developing cancer, such as esophageal squamous cell carcinoma and lung cancer, and explained the increased cancer risk by the findings that the change from T to C contributed to a decreased promoter activity of *XRCC1* leading to a diminished expression of XRCC1. It was therefore reasoned that reduced levels of XRCC1 may affect overall BER activity and hence influence the individual's risk to develop cancer (Hao et al. 2006).

XRCC1 and cancer treatment response

Several studies have sought to establish whether *XRCC1* SNPs modulate clinical outcome, but these studies have yielded mixed results. In a couple of studies, the variant allele of Arg399Gln was associated with shorter overall survival and poor prognosis in patients suffering from advanced non-small cell lung cancer (Butkiewicz et al. 2011; Gurubhagavatula et al. 2004). This finding is in line with observations by Yarosh et al. (2005) who found that cells containing the wild-type allele at position 399 of *XRCC1* were most sensitive toward a broad range of cytostatic drugs, while the variant allele conferred resistance. On the other hand, 399Gln was associated with hypersensitivity to ionizing radiation (Hu et al. 2001). Whether the SNP at position 399 might be relevant for clinical outcome is therefore not yet answered.

SNPs in poly(ADP-ribose) polymerase-1 (PARP-1)

The poly(ADP-ribose) polymerase-1 (PARP-1) is a 113-kDa nuclear protein involved in multiple cellular processes including DNA repair, genomic stability, proliferation, and cell death (Ko and Ren 2012; Langelier and Pascal 2013; Swindall et al. 2013). PARP-1 undertakes posttranslational modifications of proteins by adding poly(ADP-ribose) residues to amino acids. Various proteins involved in DNA damage repair, transcription and cell signaling are described as substrates for PARP-1 (Jungmichel et al. 2013), but the most extensively modified substrate is PARP-1 itself. Regarding DNA repair, there is strong evidence that PARP-1 participates in the repair of DNA single-strand breaks and also in the processes of BER and double-strand break (DBS) repair (Beck et al. 2014; De Vos et al. 2012). Concerning DBS repair, PARP-1 is among other a key component in an alternative non-homologous end-joining (NHEJ) pathway (A-NHEJ), which is manifested if factors of the classical NHEJ are compromised. Furthermore, PARP-1 is involved in the repair of DSBs at disrupted replication forks by competing with Ku70/ku80, resulting in DSB repair by homologous recombination (Hochegger et al. 2006; Wang et al. 2006). The degree of its participation in BER, however, is still debated (Reynolds et al. 2015; Ström et al. 2011). PARP-1 binds tightly to DNA single-strand breaks (Eustermann et al. 2011) and may also bind the single-strand break intermediate, which arises by APE1-mediated incision of abasic sites during the BER process. Following binding to single-strand breaks or single-strand break intermediates PARP-1 catalyzes the synthesis of poly(ADP-ribose) using NAD^+ as a substrate. Auto-ribosylated PARP-1 may then recruit other proteins to the strand break, including the BER protein XRCC1 (Ko and Ren 2012).

PARP-1 is encoded by the human *ADPRT* gene. Five non-synonymous SNPs have been observed in the coding region of *ADPRT*, among them the common 2446T>C leading to a substitution of alanine for valine at codon 762 (Val762Ala) (Table 1) (Cottet et al. 2000). A meta-analysis based on 39 case–control studies showed no significant association of Val762Ala with overall cancer risk (Qin et al. 2014). However, subgroup analysis on cancer types revealed that the variant allele was associated with risk of esophageal squamous cell carcinoma (Hao et al. 2004), lung cancer (Zhang et al. 2005), breast cancer (Alanazi et al. 2013), and prostate and cervical cancer in Caucasians (Lockett et al. 2004; Roszak et al. 2013). When the impact of Val762Ala on PARP-1 protein function was investigated, a reduced PARP-1 enzyme activity was observed with the variant allele 762Ala (Lockett et al. 2004; Wang et al. 2007), which may be due to a change in protein structure as hypothesized by protein prediction analysis studies (Alanazi et al. 2013). For glioblastoma, on the other hand, the variant allele of PARP-1 was associated with a 20 % reduction in cancer risk (McKean-Cowdin et al. 2009) suggesting that Val762Ala may function in a cancer-specific manner.

SNPs in nucleotide excision repair genes

Nucleotide excision repair (NER) is a highly conserved repair pathway, which recognizes and removes a wide variety of mainly bulky, helix-distorting lesions induced by UV irradiation and chemical agents (Marteijn et al. 2014; Nouspikel 2009; Schärer 2013; Shuck et al. 2008; Wood

1997). Two NER sub-pathways exist: global genome NER (GG-NER) dealing with lesions in the entire genome, and transcription-coupled NER (TC-NER), which repairs damage that blocks the elongating RNA polymerase II (de Laat et al. 1999; Fousteri and Mullenders 2008). GG-NER and TC-NER differ only in the initial step of lesion detection. Following DNA damage recognition, the two sub-pathways then converge. NER has been extensively studied over the last decades and is well documented. The repair process involves the following steps: (1) recognition of the damage and incision on both sides of a lesion, (2) excision of the damaged fragment, (3) DNA synthesis to replace the excised fragment, and (4) DNA ligation (Fig. 2). In eukaryotes, more than 30 proteins are involved in NER. The core incision reaction requires the protein factors XPC-hHR23B, XPA, RPA, TFIIH, ERCC1-XPF, and XPG (Aboussekhra et al. 1995). The major roles of XPC-hHR23B, XPA, RPA, and TFIIH factors are in damage recognition and formation of an unwound intermediate structure. The heterodimer DDB is also involved in the initial damage recognition process (Wakasugi et al. 2001). The lesion containing DNA strand is then cleaved on the 3′ side by the XPG endonuclease and the 5′ side by the ERCC1-XPF endonuclease (Evans et al. 1997a; Sijbers et al. 1996). The lesion containing oligonucleotide is removed, the gap is filled by DNA repair synthesis in a reaction catalyzed by PCNA-dependent DNA polymerase δ or ε (Wood and Shivji 1997), and the patch is sealed by a XRCC1-DNA ligase IIIα complex (Marteijn et al. 2014; Moser et al. 2007). All key components of the process have been cloned in the last decades (Friedberg et al. 2005). Mutations in NER genes lead to human disorders, namely xeroderma pigmentosum (XP), Cockayne syndrome (CS), and trichothiodystrophy (TTD), of which XP is characterized by a high incidence of skin cancer (Cleaver 2005; Lehmann 2003). In addition to the mutational changes, which result in NER deficiency and hence may lead to cancer, many SNPs have been identified in NER genes (http://egp.gs.washington.edu/ner.html). Some common NER gene SNPs will now be discussed in detail.

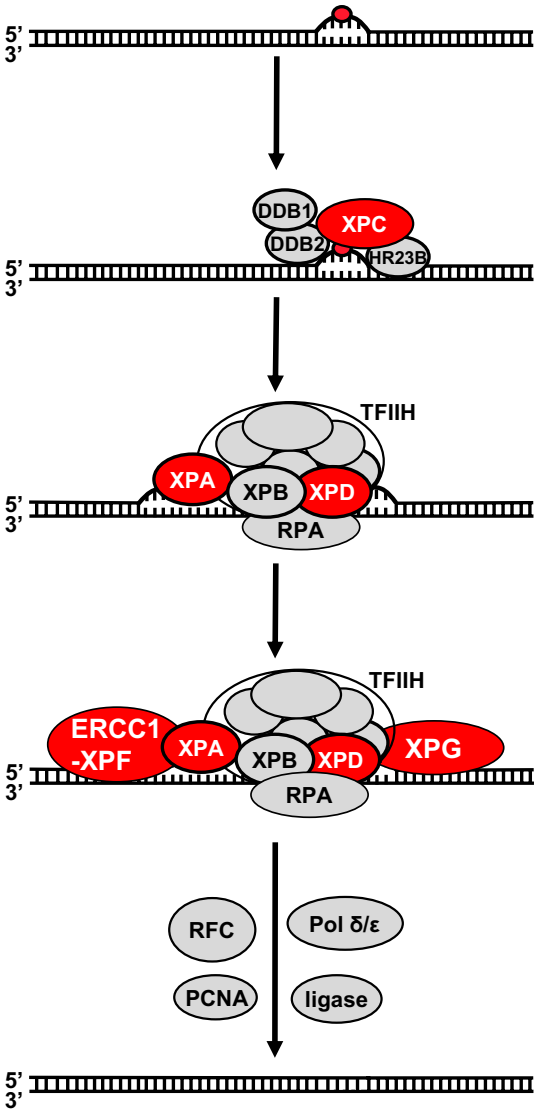

Fig. 2 Global genome nucleotide excision repair (NER). The damage-induced helix distortion is recognized by a complex of XPC-hHR23B and DDB1/DDB2. Transcription factor TFIIH with XPD among its subunits is recruited to the distortion together with RPA and XPA. The structure-specific endonuclease XPG cuts 3′ of the lesion, followed by a 5′ cut from ERCC1-XPF. The oligonucleotide containing the damage is removed and the resulting gap is filled in a polymerization reaction catalyzed by polymerase δ or ε. A ligase then seals the remaining nick. For a more detailed model of the mechanism of global genome NER and transcription-coupled NER, refer to (Marteijn et al. 2014; Nouspikel 2009). In *red*: proteins encoded by *XPC, XPA, XPD, XPF* and *XPG* for which common SNPs are described in the text

SNPs in the XPA gene

The *XPA* gene encodes for a 40-kDa protein, which is at the center of the NER machinery. XPA assists in damage recognition showing some preference for binding to damaged DNA, particularly when it is in a complex with RPA (Robins et al. 1991). Formation of the unwound intermediate structure, which precedes the dual incisions, is severely reduced in the absence of XPA, and neither the 3′ nor 5′ incision is formed (Evans et al. 1997b). In addition to interacting with DNA and RPA, XPA also physically interacts with TFIIH and ERCC1 (Park et al. 1995). Inactivating mutations in the *XPA* gene lead to severe forms of XP, with patients showing very complex clinical symptoms of an increased risk of cancer as well as neurological problems (Cleaver 2005).

Besides the XP-causing mutations, several polymorphisms are observed in the *XPA* gene. However, SNPs are

Table 2 Common single nucleotide polymorphisms (SNPs) in genes involved in nucleotide excision repair

Gene	SNP	Allele position	Residue	Variant	Frequency	Predictive analyses		SNP reference
						PolyPhen	SIFT	
XPA	G>A		Arg228	Gln	0.01	Unknown	Unknown	rs1805160
	G>T	23,446	Val234	Leu	0.01	Benign	Tolerant	
	C>G	23,500	Leu252	Val	0.01	Benign	Tolerant	
	−4G>A	1665[a]			0.38			rs1800975
XPC	XPC-PAT	1457–1461[b]						
	C>T	21,151	Ala499	Val	0.24	Benign	Tolerant	rs2228000
	A>C	33,512	Lys939	Gln	0.34	Benign	Intolerant	rs2228001
XPD	G>A	23,591	Asp312	Asn	0.24	Benign	Tolerant	rs1799793
	A>C	35,931	Lys751	Gln	0.22	Benign	Tolerant	rs13181
XPF	G>A	16,084	Arg415	Gln	0.05	Benign	Unknown	rs1800067
XPG	G>A	30,211	Arg1009	His	0.01	Benign	Tolerant	
	G>A	30,424	Arg1080	Gln	0.01	Benign	Tolerant	
	G>C	30,495	Asp1104	His	0.38	Possibly damaging	Intolerant	rs17655

[a] SNP located in the 5′ untranslated region (5′UTR) of the *XPA* gene

[b] SNP located in intron 9 of the *XPC* gene

very rare in the coding region of *XPA*. Three possible SNPs, which lead to amino acid changes, have been described, namely Arg228Gln, Val234Leu, and Leu252Val (Table 2) (Butkiewicz et al. 2000; Mellon et al. 2002; Mohrenweiser et al. 2002). To test whether the SNPs Arg228Gln or Val-234Leu have any functional effect in human cells, Mellon et al. (2002) measured cell survival and DNA repair after UV irradiation. Expression vectors containing wild-type *XPA* cDNA or cDNAs representing the SNPs have been transfected into XPA-deficient XP12RO cells. The cells complemented with the variant allele of Arg228Gln or Val-234Leu showed no decrease in TC-NER, GG-NER, or cellular survival after UV irradiation when compared to cells containing wild-type *XPA* cDNA (Mellon et al. 2002). Furthermore, when cells were treated with benzo[a]pyrene, the damage was repaired slightly more efficiently in the cells complemented with the polymorphic cDNAs (Porter et al. 2005). Taken together, the data strongly suggest that SNPs Arg228Gln and Val234Leu have no functional consequences for the cells. For Leu252Val, there is no information available regarding a possible functional effect on the XPA protein activity.

In addition, the variant alleles of Arg228Gln, Val234Leu, and Leu252Val are very rare, occurring with a frequency of ~1 % (Table 2). It therefore makes it impractical to perform epidemiological studies to investigate whether they are associated with cancer risk. For the *XPA* gene, only one SNP has been identified that occurs commonly enough for population-based case–control studies. This SNP is located in the 5′ noncoding region of the *XPA* gene. First reports claimed the SNP to be an A to G substitution located in the 5′ untranslated region at position −4 from the ATG start codon (−4A>G or A23G polymorphism) (Butkiewicz et al. 2000; Mellon et al. 2002). However, more recent analysis suggested that the major (or "wild-type" allele) at this position is the G allele. Statistics from the NIEHS SNP database and more recent published observations indicate that the G allele occurs in 62 % of individuals, while the A allele can be found in 38 % of individuals (Kiyohara and Yoshimasu 2007). Therefore, this SNP is now more commonly referred to as −4G>A or G23A polymorphism (Kiyohara and Yoshimasu 2007).

Several case–control studies have been performed to investigate whether SNP −4G>A is relevant for cancer risk, however, with conflicting results and still some confusion in the literature regarding the nature of the polymorphism. A single survey conducted by De Ruyck et al. (2007) observed no association between the −4G>A and risk of lung cancer. However, one study indicated that the A allele of −4G>A was associated with a reduced risk for lung cancer (Zienolddiny et al. 2006), while a majority of case–control studies reported a significant association of the A allele with increased lung cancer risk (Butkiewicz et al. 2004; Park et al. 2002; Popanda et al. 2004; Qian et al. 2011; Vogel et al. 2005). This observation is supported by two meta-analysis studies. Both studies describe an association between lung cancer and the presence of an A allele at −4G>A of the *XPA* gene, and it was concluded that the G allele at −4G>A protects against lung cancer (Kiyohara and Yoshimasu 2007; Liu et al. 2012). The reduced lung cancer risk was explained by a modulation in DNA repair, as Wu et al. (2003) reported a higher DNA

repair capacity (DRC) in cells with the G allele at position −4. The data, however, should be interpreted with caution, as the difference in DRC was small. Whether the −4G>A SNP has any functional effect is therefore still not known. As the SNP is localized in the so-called Kozak consensus sequence, which is crucial for the initiation of translation (Kozak 1996), it was hypothesized that a G to A transition could influence the efficiency of translation and therefore may modulate the XPA protein level of the cells. However, no such association between the *XPA* −4G>A polymorphism and changes in XPA protein levels could be detected (Butkiewicz et al. 2010). In addition, to observe any effect on cellular DNA repair, the levels of the XPA protein would have to be reduced to about 10 % of that typically found in repair proficient cells (Köberle et al. 2006). Therefore, whether the −4G>A polymorphism is functionally significant still needs to be clarified.

As described above, the A allele of −4G>A has been linked to lung cancer in numerous studies. Similarly, the risk of esophageal squamous carcinoma is reported to be associated with the A allele (Guo et al. 2008), as it is also the case for gastric cancer, when combined with a polymorphism in the *XPC* gene (Palli et al. 2010). On the other hand, the risk of endometrial cancer was reduced when the A allele was present, but only among women who had used oral contraception (Weiss et al. 2006). For basal and squamous cell carcinoma of the skin, an increased risk was seen when the common G allele was present (Miller et al. 2006). This has been observed for colorectal cancer, breast cancer, and cancer of the head and neck (Liu et al. 2012).

Taken together, as the data of the epidemiological studies conflict with one another, we believe that the *XPA* −4G>A polymorphism should not be used to predict a general cancer risk but might be a useful marker for specific types of cancer.

Common SNPs in the XPD gene

The *XPD* gene product is one of ten subunits of the basal transcription factor TFIIH and plays an important role in both transcription and NER (Friedberg et al. 2005; Giglia-Mari et al. 2004). XPD is an 87-kDa protein with helicase activity, which unwinds DNA in the 5′–3′ direction (Coin et al. 2007; Schaeffer et al. 1994). Mutations in the *XPD* gene can result in a reduction of the helicase activity, which might affect NER and/or basal transcription leading to the human disorders already described (Cleaver 2005; Lehmann 2003). In addition to mutations, many SNPs have been reported within the *XPD* gene, most of them in noncoding intron regions. Five polymorphisms have been observed in the coding region of *XPD* (Broughton et al. 1996). Of those, two were found to lead to a change of amino acids (Asp312Asn and Lys751Gln), while the others have no effect on the amino acid sequence (Table 2). Variants of both Asp312Asn and Lys751Gln are common, with an allele frequency of 24 % for the Asn allele at residue 312 and 22 % for the Gln allele at residue 751. These SNPs have been investigated in numerous case–control studies for a possible link to cancer risk, however, with mixed results.

One investigation reported that for breast cancer the frequencies of the variant allele 312Asn were significantly higher in cancer patients compared to the control group (Hussien et al. 2012). Other studies, however, found no link between Asp312Asn and/or Lys751Gln variants and the incidence of breast cancer (Jorgensen et al. 2007; Kuschel et al. 2005). A meta-analysis performed on data of 40 individual studies also concluded that no clear association can be found between breast cancer and *XPD* SNPs, ruling out polymorphisms of *XPD* as a risk factor for this kind of cancer (Pabalan et al. 2010). The positive result of Hussien and co-workers might be due to the relatively small sample size of the study, which might have overestimated a possible cancer risk.

Studies of Asp312Asn or Lys751Gln have also failed to find an association with melanoma (Povey et al. 2007; Winsey et al. 2000), non-Hodgkin's lymphoma (Worrillow et al. 2009), acute lymphoblastic leukemia (Batar et al. 2009), endometrial cancer (Weiss et al. 2006), bladder cancer (Shen et al. 2003; Stern et al. 2002), and colon cancer (Mort et al. 2003). In a recent meta-analysis, no correlation between Lys751Gln and the risk os laryngeal cancer was found (Li et al. 2016). On the other hand, XPD variants 312Asn and 751Gln have been associated with squamous cell carcinoma of head and neck (Sturgis et al. 2000), and for 312Asn a moderate risk of prostate cancer was observed (Rybicki et al. 2004). These findings, however, were not confirmed by other studies (Hu et al. 2012; Lockett et al. 2005).

The situation regarding lung cancer is similarly confusing. *XPD* SNPs have been most extensively studied as possible risk factors for the development of lung cancer, the studies, however, have yielded mixed results. An increased risk of lung cancer has been reported for the variant alleles of Asp312Asn or Lys751Gln (De Ruyck et al. 2007; Liang et al. 2003; Xing et al. 2002; Zienolddiny et al. 2006), with the higher risk affecting mostly light smokers and non-smokers (Butkiewicz et al. 2001; Qian et al. 2011). However, other studies report that there is no association between *XPD* SNPs and lung cancer (David-Beabes et al. 2001). A number of meta-analyses were done on published data from individual case–control studies about a possible link between *XPD* SNPs and lung cancer risk. While one of the studies suggested that the 312Asn and 751Gln variant alleles are associated with an increased risk of lung cancer (Hu et al. 2004); another meta-analysis concluded that no

clear association can be found between the two *XPD* SNPs and lung cancer (Benhamou and Sarasin 2002). Altogether, to date it is still controversial whether there is a causal relationship between *XPD* SNPs and increased lung cancer risk.

It is also questionable whether the protein changes at residues 312 and 751 have any effect on the cellular repair capacity. Based on analyses of evolutionary alignments, Clarkson and Wood predicted that it is unlikely that the two *XPD* SNPs will have functional consequences (Clarkson and Wood 2005). SIFT and PolyPhen predictive analyses for the two *XPD* SNPs also predict that both SNPs are tolerated/benign (Table 2).

Clarkson and Wood also critically evaluated a number of published studies which investigated the impact of the two common *XPD* SNPs at codon 312 and codon 751 on cellular DNA repair capacity but found no convincing evidence for any functional effects of the *XPD* SNPs on DNA repair (Clarkson and Wood 2005). Seker et al. (2001) transfected plasmids containing cDNA for *XPD* wild type or variants for codon 312 or 751 into a lymphoblastoid cell line from an XP-D patient and assessed the effect on the DNA repair capacity using the host cell reactivation assay. They observed that the plasmids containing the sequence variations were able to complement the mutated *XPD* gene and restore repair, similar to *XPD* wild type. Obviously, sequence variations at codon 312 and codon 751 do not alter the cellular capacity for DNA repair. This conclusion is supported by studies of Laine et al. (2007) who applied recombinant TFIIH complexes containing the XPD variants 312Asn or 751Gln in in vitro assays to directly investigate the effect of these variants on DNA repair and basal transcription. Compared to wild-type XPD, variants 312Asn or 751Gln did not show significant differences neither for their repair nor for their transcriptional activities in vitro, which is a strong indication that the two *XPD* SNPs at codon 312 and codon 751 do not affect the function of the protein.

In summary, based on epidemiological data and observations concerning the functional impact, it would appear that the described *XPD* SNPs do not constitute a major risk for developing cancer.

SNPs in NER genes XPC, XPF and XPG

Single nucleotide polymorphisms have also been identified in genes of other XP groups, such as XP-C, XP-F, and XP-G (Table 2). *XPC* encodes for the 106-kDa XPC protein, which is involved in the initial damage recognition step of the NER process (Batty and Wood 2000; Sugasawa et al. 1998). XPC is tightly bound to its partner hHR23B (Masutani et al. 1994). XPC-hHR23B appears to detect and bind to helical distortions caused by DNA damage, which may initiate the NER process (Batty and Wood 2000). XPC-hHR23B is also essential for the recruitment of the remaining components of the NER machinery to the damaged site (Yokoi et al. 2000). For the *XPC* gene, several SNPs have been identified, with three of them being commonly studied. A 83-bp insertion consisting of A and T residues together with a 5-bp deletion (GTAAC) is often observed in intron 9 of the *XPC* gene resulting in an intronic, biallelic poly (AT) insertion/deletion polymorphism (*XPC*-PAT) at this position (Khan et al. 2000) (Table 2). For squamous cell carcinoma of head and neck, it was observed that the frequency of the *XPC*-PAT allele was higher in patients compared to control individuals, suggesting that *XPC*-PAT may contribute to an increased risk of developing this kind of cancer (Shen et al. 2001). Similarly, Marin et al. (2004) reported a significantly increased risk of lung cancer when the *XPC*-PAT allele was present. Using host cell reactivation assays to investigate for functional significance, *XPC*-PAT was shown to be associated with a small variation for DNA repair capacity (Qiao et al. 2002), and the reduced repair capacity was suggested to contribute to the increased risk of lung cancer (Khan et al. 2000; Marin et al. 2004). Other studies, however, did not report a significant association between *XPC*-PAT and the risk of lung cancer (De Ruyck et al. 2007; Lee et al. 2005). Altogether, due to the inconsistent data, it is therefore questionable whether the *XPC*-PAT allele could be used as a marker for cancer development.

Among the SNPs, which have been identified in the coding sequences of *XPC*, two are commonly studied: Ala499Val and Lys939Gln. An increased risk for developing bladder cancer was found for variant alleles 499Val and 939Gln (Qiu et al. 2008; Rouissi et al. 2011; Sak et al. 2006; Sanyal et al. 2004). The variant 499Val was also connected to an increased risk of gall bladder cancer, while in this case the variant form of Lys939Gln does not seem to be a risk factor (Jiao et al. 2011). No significant association between 939Gln and cancer was also observed for colorectal cancer (Gil et al. 2012). Studies investigating a possible link between Lys939Gln and lung cancer risk have yielded conflicting results. On the one hand, no significant association was found for the variant allele 939Gln and lung cancer (Hu et al. 2005). On the other hand, a meta-analysis performed on Lys939Gln identified the 939Gln allele as a risk factor for lung cancer (Qiu et al. 2008).

ERCC1-XPF is the structure-specific endonuclease, which cuts the damaged DNA strand during the NER process on the 5′ side of the lesion (Sijbers et al. 1996). *XPF* encodes for the ~104-kDa XPF subunit, which forms a tight complex with its partner ERCC1 (Biggerstaff et al. 1993). Mutations in *XPF* result in xeroderma pigmentosum complementation group XP-F, which is clinically characterized by mild symptoms and a later age of onset of skin

cancer (Matsumura et al. 1998). Furthermore, numerous SNPs have been identified in the *XPF* gene. Seven possible *XPF* SNPs, which lead to amino acid changes, have been observed (http://egp.gs.washington.edu/ner.html). A number of case–control studies have been performed to investigate for a possible link between *XPF* SNPs and different types of cancers, with most of these studies focusing on SNP Arg415Gln (Table 2). The results, however, are inconclusive. This might be explained by relatively small sample sizes of the studies, as the variant allele 415Gln is very rare (~5 %). No association between the variant form of Arg415Gln and cancer risk has been observed with laryngeal cancer (Abbasi et al. 2009), lung cancer (Hung et al. 2008) and breast cancer (Pei et al. 2014). A meta-analysis conformed that overall the risk of breast cancer is not elevated by the variant allele 415Gln but subgroup analyses by ethnicity revealed an increased risk of breast cancer in the Caucasian ethnicity (Ding et al. 2011). A meta-analysis performed on data of 43 case–control studies confirmed the lack of a significant association between *XPF* Arg415Gln and overall cancer risk; moreover, when analyses by cancer type, ethnicity, or sample size were preformed, no significant association with cancer risk was observed in any of the subgroups (Shi et al. 2012). Altogether, based on the data obtained to date, it would appear that *XPF* SNP Arg415Gln does not constitute a major risk for developing cancer.

The *XPG* gene encodes for a 133-kDa structure-specific endonuclease which cleaves damaged DNA ~5 nucleotides 3′ to the site of the lesion (O'Donovan et al. 1994). Mutations in the *XPG* gene result in the XP phenotype as well as in a phenotype that combines features of XP and CS. A number of polymorphisms have been identified in the *XPG* gene, including SNPs that lead to the changes Arg1009His, Arg1080Gln, and Asp1104His (Emmert et al. 2001). While variants of Arg1009His and Arg1080Gln are very rare (~1 %), Asp1104His is a common polymorphism and has been investigated in a number of population-based case–control studies. The variant allele 1104His has been associated with cancer at several sites, such as cervical carcinoma (He et al. 2008), prostate cancer (Berhane et al. 2012), lung cancer, and squamous cell carcinomas of the oropharynx, larynx, and esophagus (Cui et al. 2006; Jeon et al. 2003). Regarding breast cancer, the frequency of the variant allele was marginally but significantly increased in patients (Kumar et al. 2003). Solely for bladder cancer, the Asp1104His SNP does not seem to play a role (Rouissi et al. 2011). Altogether, based on the epidemiological observations, the *XPG* Asp1104His SNP might serve as a genetic marker for susceptibility to cancer.

However, it is not yet clear whether the amino acid substitution at residue 1104 directly affects the function of XPG. SIFT and PolyPhen analyses predict this SNP to be possibly damaging/intolerant (Table 2). On the other hand, no significant differences in in vivo repair kinetics for removal of UV induced lesions were found between individuals carrying different genotypes at position 1104 (Kumar et al. 2003). Therefore, as it is not yet established whether this SNP directly affects the activity of the XPG protein, no predictions about the impact on protein function should be drawn.

SNPs in NER genes and cancer treatment response

Based on the assumption that SNPs in NER genes can alter the protein activity and hence influence the capacity of nucleotide excision repair, it was hypothesized that these SNPs not only increase the susceptibility to carcinogenesis but may also affect the response to cancer treatment, as DNA lesions induced by chemotherapeutic drugs are often repaired by NER (Zamble and Lippard 1995). As discussed in "SNPs in the XPA gene" to "SNPs in NER genes XPC, XPF and XPG" section, it should be noted that there is no convincing evidence that SNPs in NER genes actually affect the NER activity. Nevertheless, there are numerous studies investigating the effect of NER gene SNPs on response to chemotherapy, however, with mixed results. In one study, the possible association between treatment response in women with advanced ovarian epithelial cancer and SNPs in the NER genes *XPA*, *XPC*, *XPD* and *XPG* was assessed (Saldivar et al. 2007). Based on the response to platinum chemotherapy, patients were classified as "responders" and "non-responders." This study observed no statistical significant association between treatment response and NER gene SNPs, with the lack of statistical significance being explained by low sample sizes (Saldivar et al. 2007). However, the variant genotype of *XPG* Asp1104His appeared to negatively affect the median survival time of the ovarian cancer patients (Saldivar et al. 2007). For patients with small cell lung cancer, who were treated with cisplatin-based combination chemotherapy, no statistically significant difference in response or survival was found relating to XPD variants Asp312Asn and Lys751Gln (Ryu et al. 2004). Contradictory to these observations, another study linked the XPD variant 312Asn to a decreased overall survival in lung cancer patients treated with cisplatin or carboplatin. Based on these findings, the authors proposed to use Asp312Asn as a prognostic marker to identify lung cancer patients who might benefit from clinical trials involving novel drugs other than platinating agents (Gurubhagavatula et al. 2004). Park et al. (2001) reported that in patients with metastatic colorectal cancer the *XPD* variant allele of Asp312Asn was not linked to response to oxaliplatin/5-fluoruracil chemotherapy or overall survival, while the variant allele of Lys751Gln

was associated with a reduced response to treatment and a significantly shorter survival suggesting that XPD Lys-751Gln may be an important marker to predict the clinical outcome to chemotherapy for that specific type of cancer. For acute myeloid leukemia, it was also assumed that Lys-751Gln modulates the clinical outcome (Allan et al. 2004). A recent study by Lopes-Aguiar et al. (2016) investigated the effect of SNPs in the NER genes *XPC*, XPD, *XPF*, and *ERCC1* on treatment with cisplatin and reported a correlation between the variant allele of *XPD* Asp312Asn and reduced progression-free survival and overall survival in patients with head and neck squamous cell carcinoma. An association with response to platinum chemotherapy was also reported for the *XPA* SNP −4G>A, as the G allele at this position was linked to increased response to cancer treatment in patients with advanced non-small cell lung cancer (Feng et al. 2009). Taken together, even though some studies claim that SNPs in NER genes may modulate cancer treatment, no clear association between NER SNPs and cancer treatment response can be established to date. In addition as it is assumed that SNPs in NER genes can alter protein activity and might therefore lead to a reduced NER capacity, one would expect an increased response to chemotherapy with DNA-damaging agents. As the contrary has been observed in all of the studies described in this section, it is difficult to envisage a mechanism of how SNPs in NER genes might modulate cancer treatment. We therefore suggest that even though NER SNPs might be important prognostic markers to predict the efficacy of chemotherapeutic therapy they should be used with caution to predict the clinical outcome.

SNPs in double-strand break repair genes

DNA double-strand breaks (DSBs) may arise either spontaneously during replication or as a consequence of exposure of cells to DNA-damaging agents such as ionizing radiation. Unrepaired or mis-repaired DSBs are highly cytotoxic and may lead to genomic instability and cancer. Two general types of DSB repair exist: homologous recombination (HR) and non-homologous end-joining (NHEJ) (Fig. 3a, b) (Davis and Chen 2013; Haber 2000; Takata et al. 1998; Wyman and Kanaar 2006). NHEJ appears to be the major pathway for repairing DSBs, whereas HR is restricted on removal of a portion of DSBs occurring in the late S phase/G2 phase of the cell cycle (Beucher et al. 2009; Thacker 2005). Following introduction of a DSB, a cascade of reactions is triggered, leading to the recruitment of repair factors at the site of the damage. Whether HR or NHEJ is used for repair of the DSB appears to be regulated during the cell cycle (Haber 2000; Kakarougkas and Jeggo 2014).

SNPs in genes of homologous double-strand break repair

The key components of HR repair have been identified in the last decades. An important role is played by the *RAD51* family of genes and *Rad51*-like genes, among them *XRCC3* (Thacker 2005). The *XRCC3* gene encodes for the 37-kDa XRCC3 protein, which is supposed to maintain chromosomal stability during the repair process (Liu et al. 1998; Pierce et al. 1999; Thacker 2005). Two SNPs, which lead to a change in amino acids, have been identified in *XRCC3* (Table 3). The variant form of Thr241 Met is occurring commonly enough for population-based case–control studies. A meta-analysis of 48 case–control studies reported that the variant Thr241 Met allele is associated with a slightly increased cancer risk in general, and the effect seems to be tissue dependent (Han et al. 2006). The 241Met allele has been implicated with melanoma (Winsey et al. 2000), thyroid cancer (Sturgis et al. 2005), bladder cancer (Matullo et al. 2001a), colorectal cancer (Krupa et al. 2011), brain tumors (Custodio et al. 2012), and breast cancer (He et al. 2012). Investigation of DNA damage in lymphocytes indicated that carriers of the 241Met allele had higher DNA damage levels compared to control individuals, and it was suggested that the variant allele of Thr241Met is associated with a low DNA repair capacity (Matullo et al. 2001b). Danoy et al. (2007) performed functional analysis studies to assess whether the Thr241Met polymorphism has any effect on DNA damage induced by DNA cross-linking agents. In these experiments expression constructs containing either *XRCC3* wild-type cDNA or the cDNA representing the variant allele for codon 241 were transfected into XRCC3 deficient DT40 chicken cells and the sensitivity toward cisplatin or mitomycin C was assessed using colony formation. DT40 cells were shown to be significantly impaired in their potential to perform homologous recombination (Takata et al. 2001). As DT40 cells complemented with the 241Met allele showed similar sensitivity compared to cells with wild-type cDNA, it seems that SNP Thr241Met does not have any significant effect on DNA damage repair (Danoy et al. 2007). In addition, several studies failed to find an association between variant allele 241Met and different types of cancer such as lung cancer (David-Beabes et al. 2001), colon carcinoma (Tranah et al. 2004), head and neck cancer (Gresner et al. 2012), and breast cancer (Romanowicz-Makowska et al. 2011; Silva et al. 2010). A meta-analysis performed on Thr241Met and gastric cancer observed no overall cancer risk connected to the variant allele (Fang et al. 2011). However, in a subgroup analysis based on ethnicity, the variant allele was associated with an increased cancer risk in Caucasians, but decreased cancer risk in Asians (Fang et al. 2011). Another SNP in the *XRCC3* gene is Arg94His,

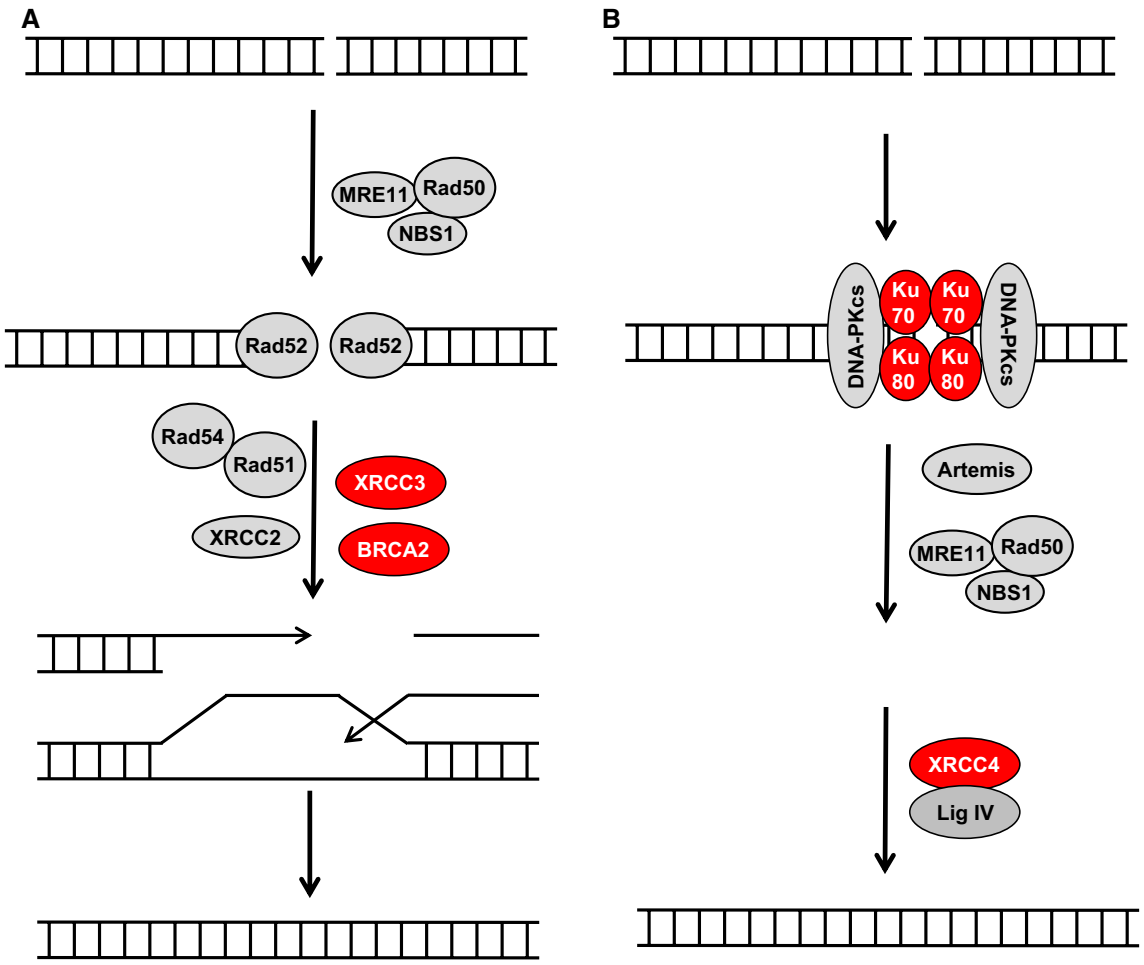

Fig. 3 Double-strand break repair. **a** Homologous recombination (HR). At the double-strand break a 3′ end for the Rad51, Rad52 proteins are generated by a complex of Rad50/Mre11/NBS1. Rad54, XRCC2, XRCC3, BRCA2 and Rad51 paralogs participate in the following strand invasion, branch migration and resolution of Holliday junctions. **b** Non-homologous end-joining (NHEJ). Non-homologous end-joining is performed by a complex of Ku70, Ku80, and DNA-PKcs, which binds to the end of a double-strand break. Ligase IV and XRCC4 complete the repair event. Other factors such as Artemis, Rad50/Mre11/NBS1 complex are also involved. In *red*: proteins encoded by *XPCC3, BRCA2, XRCC4, XRCC5*, and *XRCC6* for which common SNPs are described in the text

which is very rare and the information about a possible link to cancer risk is limited. Only one study implicated the variant allele 94His with head and neck cancer (Gresner et al. 2012).

BRCA2 also functions in the HR process (Krejci et al. 2012; Venkitaraman 2002). It acts by binding to single-stranded DNA and interacting with Rad51 to stimulate strand invasion, a vital step of homologous recombination (Davies et al. 2001; Yang et al. 2002). Several SNPs leading to amino acid changes have been characterized in the *BRCA2* gene, with most of them occurring very seldom (~ 1 %). In a number of epidemiological studies, some of the *BRCA2* SNPs have been evaluated in relation to cancer risk. As *BRCA2* is a known breast cancer susceptibility gene (Martin and Weber 2000), most studies have focused on the relevance of *BRCA2* SNPs for this type of cancer, however, with contradictory results. The variant allele of Asn372His has been reported to be associated with an increased risk for breast cancer (Healey et al. 2000; Spurdle et al. 2002). A link to breast cancer has also been observed for the variant alleles of Met784Val (Ishitobi et al. 2003) and Asn991Asp (Loizidou et al. 2009). However, other studies report that there is no significant association of BRCA2 SNPs to breast cancer risk (Baynes et al. 2007; Freedman et al. 2004; Garcia-Closas et al. 2006). Numerous studies have shown that BRCA2 is implicated in hereditary breast cancer as individuals carrying mutations in *BRCA2* have an increased risk for cancer development (Cavanagh and Rogers 2015; King et al. 2003). As described above the epidemiological data are variable and therefore do not allow to answer the question of whether polymorphisms in *BRCA2* are also relevant for breast

Table 3 Common single nucleotide polymorphisms (SNPs) in genes involved in double-strand break repair

Gene	SNP	Allele position	Residue	Variant	Frequency	Predictive analyses		SNP reference
						PolyPhen	SIFT	
XRCC3	C>T	18,085	Thr241	Met	0.22	Benign	Intolerant	rs861539
	G>A	10,371	Arg94	His	0.03	Benign	Tolerant	rs3212057
BRCA2	A>C	18,341	Asn372	His	0.26	n.a.[a]	n.a.	rs144848
	A>G	22,454	Met784	Val	0.01	n.a.	n.a.	
	A>G	23,075	Asn991	Asp	0.05	n.a.	n.a.	rs799944
XRCC4	G>T	128,782	Ala247	Ser	0.02	n.a.	n.a.	rs3734091
	−651/−652 T>G	1394[b]			0.01			rs2075685
								rs6869366
	C>T	1475[c]			0.01			rs2075686
XRCC6	C>G	−1310[d]			0.28			rs2267437
	G>T	1781	Gly593	Gly	0.23	n.a.	n.a.	rs132788
XRCC5	G>A	2099–2408[e]			0.1			rs3835
	T>A							rs9288516

[a] n.a., no SIFT/PolyPhen predictions available

[b] SNP located in the 5′ untranslated region (5′UTR) of the *XRCC4* gene

[c] SNP located in the 5′ untranslated region (5′UTR) of the *XRCC4* gene

[d] SNP located in front of the promoter start of the *XRCC6* gene

[e] SNP located in intron 19 of the *XRCC5* gene

cancer risk. For follicular lymphoma, a subtype of non-Hodgkin's lymphoma, *BRCA2* SNP Asn372His, is implicated in cancer development (Salagovic et al. 2012). For thyroid cancer, on the other hand, neither Asn372His nor Asn991Asp had an influence on cancer development (Sturgis et al. 2005). Altogether, based on the inconsistent data, it is difficult to speculate on *BRCA2* SNPs as risk factors for cancer development.

SNPs in genes of non-homologous end-joining

The second main pathway by which DSBs are repaired is by non-homologous end-joining (NHEJ), which involves the rejoining of the broken DNA ends. Several of the genes taking part in NHEJ have been identified and their protein products characterized. The process requires as a minimum the core factors Ku70, Ku80, XRCC4, DNA-PKcs, and DNA ligase IV (Fig. 3) (Davis and Chen 2013; Haber 2000). XRCC4 has been shown to interact directly with Ku70 and Ku80 and is suggested to serve as a link between Ku70/80 and ligase IV (Mari et al. 2006). Five non-synonymous SNPs have been found in the *XRCC4* gene (Table 3). However, as these SNPs are rare, only limited data are available investigating for a possible relationship between SNP and cancer risk. For Ala247Ser no association between the variant allele and bladder cancer was observed (Chang et al. 2009). Similarly, a meta-analysis of published studies on lung cancer failed to find an association between this type of cancer and a number of *XRCC4* SNPs (Yu et al. 2011). In addition to SNPs in the coding region of *XRCC4*, numerous SNPs have been identified in noncoding sequences of *XRCC4* such as the promoter region and the introns. The information about these SNPs is, however, somewhat confusing as to the nature of the SNP, the exact location and the respective SNP reference. A number of SNPs are reported to be located in the promoter region of *XRCC4*, and it was investigated whether SNPs in the promoter region would influence the transcriptional activity and hence the susceptibility to cancer development. At position −651/−652 of the *XRCC4* promoter a SNP for T/G has been reported, for which the SNP references rs6869366 or rs2075685 have been assigned. Yu et al. (2011) generated luciferase reporter gene constructs containing 1000 bp of the *XRCC4* promoter region with either G or T at position −651 and reported a significantly higher reporter gene expression when T was present. As this effect has been observed in the cervical cancer cell line HeLa, the lung carcinoma cell line H1299 and the colon carcinoma cell line HCT116 the authors suggested that the G to T allele change leads to an increase in promoter activity in a non-tissue-specific manner (Yu et al. 2011). However, Shao et al. (2014) reported higher luciferase activities connected to the G allele at position −652T>G when prostate cancer cell lines were used. Therefore, neither the exact position of SNPs in the promoter region nor the effect on transcriptional activity is yet clear. Investigations for a

possible link between −561/−562 SNP (rs2075685) and cancer risk also yielded conflicting data. While the T allele was associated with a higher risk of breast cancer (Fu et al. 2003) and pancreatic cancer (Shen et al. 2015), the G allele was associated with bladder cancer (Chang et al. 2009). However, a meta-analysis of data from published studies of different cancer types failed to find any association of rs2075685 with cancer risk (Shao et al. 2012/2013). Data on additional SNPs, also located in noncoding sequences of XRCC4 are similarly inconsistent, reporting a possible contribution to cancer susceptibility (Figueroa et al. 2007; Hayden et al. 2007; Shao et al. 2012/2013) or no effect on cancer risk (Chang et al. 2009; Shao et al. 2012/2013). A summary of studies investigating a possible association between *XRCC4* SNPs and risk of multiple cancers is given by Wu et al. (2008).

The proteins Ku70 and Ku80 are encoded by *XRCC6* and *XRCC5*, respectively. Regarding SNPs in *XRCC6* and *XRCC5* and cancer risk, only limited information is available. The variant allele of −1310 C>G, which is located in front of the promoter start of *XRCC6*, has been reported as a risk allele for breast cancer (Fu et al. 2003; Willems et al. 2008, 2009), while for 2099–2408 G>A of *XRCC5*, no significant effect on breast cancer risk was observed (Fu et al. 2003). The synonymous SNP at allele 1781 G>T of *XRCC6,* underlying Gly593Gly, seemed to protect against breast cancer (Willems et al. 2008) or showed no effect on cancer risk (Fu et al. 2003). In addition, rs9288516 of *XRCC5* was connected to decreased risk of brain tumors (Jin et al. 2015) but increased risk of liver cancer (Li et al. 2011), while no clear association of *XRCC6* SNPs and liver cancer was observed (Li et al. 2011).

Concluding remarks

A significant number of SNPs has been characterized in DNA repair genes, some of them leading to a change in the amino acid sequence of the respective protein. It therefore has been hypothesized that these so-called non-synonymous SNPs might affect the cellular DNA repair capacity and in turn might increase the likelihood that cancer will develop. A number of epidemiological studies have reported an association between specific SNPs and certain types of cancer, while other investigations failed to do so. In addition, there is little evidence that SNPs in DNA repair genes have an impact on protein function and will lead to proteins with functional deficiency. However, if a specific SNP occurs more frequently in a cancer population than in control group, this SNP may be linked to cancer risk and might be used as a genetic marker. It is, however, important to remember that a possible association between SNP and cancer risk does not imply the SNP to be functionally significant. This is illustrated by a synonymous SNP in the *XPD* gene, which has no effect on the protein sequence of XPD, but the variant allele at position 156 has been associated with an increased risk of bladder cancer (Shao et al. 2007). Altogether, to better understand the biological relevance of different SNPs, more functional experiments are required.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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