Chapter 9

Homologous Recombination Repair Polymorphisms, Cancer Susceptibility and Treatment Outcome

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Additional information is available at the end of the chapter

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1. Introduction

DNA repair mechanisms are crucial for the maintenance of genome's integrity. When DNA damage is not repaired promptly, that may pose a serious threat to genomic stability and can contribute to carcinogenesis. On the other hand, the core molecular mechanism of action in several cancer treatments including chemotherapeutic agents and radiation therapy is induction of DNA damage and the efficacy of DNA repair mechanisms may influence the outcome of cancer treatment. Genetic variability of DNA repair proteins can modify the ability to repair DNA damage and may therefore play an important role in both cancer susceptibility and the outcome of cancer treatment.

DNA damage arises from exposure to endogenous or exogenous factors, including chemotherapeutic agents and radiation therapy [1]. There are several forms of DNA damage and therefore several mechanisms involved in their repair. Complex changes such as double strand breaks (DSBs) can lead to chromosome loss, chromosomal rearrangements or apoptosis and as a result can have a significant impact on cellular processes. DSBs represent one of the most detrimental forms of DNA damage because both strands of DNA are damaged and are thus especially challenging for efficient and accurate DNA repair [2]. One of the important pathways involved in DSB repair is HRR, a complex mechanism consisting of several steps that requires coordinated interplay of various enzymes [3]. This chapter focuses on homologous recombination repair (HRR) and summarizes the current knowledge on how genetic variability in this pathway influences cancer susceptibility and treatment outcome.

2. Homologous recombination repair pathway

HRR is crucial for the repair of DSBs, but is also involved in repair of other types of DNA damage, such as interstrand crosslinks. HRR ensures complete repair of DSBs because the undamaged homologous chromosome serves as a template to repair the damage.

In the first step of HRR, MRN complex is essential for recognition of DSBs. MRN complex consists of three proteins: meiotic recombination 11 homologue (MRE11), DNA repair protein RAD50 (RAD50) and nibrin (NBN). MRN recruits different enzymes to the site of DNA damage and activates them [4]. In the beginning, the broken ends of DSBs are processed to single stranded 3′ ends. DNA repair protein RAD51 homolog 1 (RAD51) then binds to DNA and forms a nucleoprotein filament. With the help of mediator proteins such as X-ray repair cross-complementing group 3 (XRCC3) and XRCC2, RAD51 catalyses the central reaction of HRR: the search for a homologous template and strand transfer between the damaged region and the undamaged homologous chromatid. The 3′ end of the damaged strand invades the homologous chromatid and is elongated by DNA polymerase using the complementary strand of the homologous chromatid as a template, resulting in the formation of Holliday junctions. After resynthesis and ligation of the damaged region, resolvase is needed for the resolution of Holliday junctions. Resolution can lead to either crossover or non-crossover products, but it always results in two intact double-stranded DNA molecules [5].

3. Genetic variability in homologous recombination repair genes

DNA repair mechanisms can be less effective in some individuals, leading to increased cancer susceptibility. Rare mutations in DNA repair genes that result in decreased DNA repair capacity have been linked to different hereditary cancers. DNA repair capacity may also be influenced by genetic polymorphisms that were identified in these genes. In particular, common functional single nucleotide polymorphisms (SNPs) leading to amino acid substitutions as well as SNPs in promoter or miRNA binding sites may influence the activity, stability or expression of DNA repair proteins.

The majority of cancer susceptibility and pharmacogenetic studies related to HRR has focused on genetic variability of *NBN*, *RAD51*, *XRCC2*, and *XRCC3*. Most commonly investigated SNPs in these genes, their predicted function and their minor allele frequencies (MAFs) in population of European descent are presented in Table 1.

3.2. *NBN*

MRN complex is involved in DSB recognition in different repair pathways, not only in HRR [14], suggesting that NBN may play a crucial part in DNA repair. NBN consists of three functional regions [6]. The N-terminal region binds to phosphorylated histone H_2AX (γ-H_2AX) and allows the MRN complex to move close to the sites of DSBs [6]. The central region is involved in signal transduction for damage response, while the C-terminal region is involved in MRE11 binding.

Gene	rs number	Polymorphism	Location	Predicted function	MAF[a]
NBN	rs1805794	p.Glu185Gln	Exon, nonsynonymous	Affects interaction with BRCA1 [6]	0.304
	rs709816	p.Asp399Asp	Exon, synonymous	Affects splicing [7]	0.357
	rs1063054	c.*1209A>C	3′ UTR	Affects miRNA binding [8]	0.317
	rs2735383	c.*541G>C	3′ UTR	Affects miRNA binding [8-10]	0.312
RAD51	rs1801320	c.-98G>C	5′ UTR	Enhances promoter activity [11]	0.067
	rs1801321	c.-61G>T	5′ UTR	Enhances promoter activity [11]	0.467
XRCC3	rs1799794	c.-316A>G	5′ UTR	Affects transcription factor binding [8]	0.184
	rs861539	p.Thr241Met	Exon, nonsynonymous	Might affect protein structure or function [12]	0.433
XRCC2	rs3218536	p.Arg188His	Exon, nonsynonymous	Modified sensitivity to DNA damaging agents [13]	0.094

[a]MAF: minor allele frequency in population of European descent included in HapMap project (HapMap-CEU)

Table 1. Most commonly investigated HRR SNPs and their predicted function.

Mutations in the *NBN* gene may lead to autosomal recessive disorder Nijmegen breakage syndrome, presenting with immunodeficiency, increased cancer risk and radiation sensitivity [6]. Rare *NBN* mutations were associated with chromosomal instability and increased susceptibility to cancer [15] and are presented in Table 2. The most common is a deletion of five nucleotides (675del5), common in Slavic populations [16], that leads to protein truncation [17].

Mutation	rs number	Predicted function
Asp95Asn	rs61753720	May affect protein-protein interactions [18], not highly damaging [19]
Ile171Val	rs61754966	Affects protein structure and protein-protein interactions [20]
Arg215Trp	rs61753718	Impairs histone γ-H_2AX binding [4]
Pro266Leu	rs769420	Probably damaging effect [8]
657del5		Leads to protein truncation [17]

Table 2. Most common mutations in the *NBN* gene.

Besides rare mutations, several common SNPs have been described in both the coding region and the regulatory regions of *NBN* gene (Table 1). By far the most frequently investigated

polymorphism is *NBN* rs1805794 (p.Glu185Gln) that leads to amino acid change in BRCA1 C-terminal domain [6] and could therefore affect protein-protein interactions with other HRR proteins. Polymorphic rs1805794 C allele was previously associated with decreased DNA damage detected with comet assay in healthy individuals [21]. It was also shown to modify the frequencies of chromatid-type aberrations [22]. *NBN* rs709816 (p.Asp399Asp) is a synonymous SNP that does not change the amino acid sequence in the central region of NBN. Two other *NBN* SNPs that may be functionally important, rs2735383 (c.*541G>C) and rs1063054 (c.*1209A>C), are located in the 3′ untranslated region (UTR). Rs1063054 was predicted to affect miRNA binding, but that was not yet validated [4, 8]. On the other hand, studies have already shown that rs2735383 modifies miR-629 and miR-509-5p binding and the polymorphic C allele was associated with lower transcriptional activity [9, 10].

3.2. *RAD51*

RAD51 is a key enzyme of HRR that has both DNA binding and ATPase activities. It interacts with many proteins, for example RAD51 paralogs, BRCA1, BRCA2 and RAD54 [23]. Several SNPs have been described in *RAD51* gene, but only few are located in the coding region. On the other hand, there are SNPs in the 5′ UTR that may affect both gene transcription and protein expression, such as *RAD51* rs1801320 (c.-98G>C) and rs1801321 (c.-61G>T) that were reported to increase promoter activity [11, 24]. *RAD51* rs1801320 polymorphism was also associated with protein over-expression and increased DNA repair [11]. The polymorphic rs1801321 allele facilitates binding of a transcription factor, thus increasing the transcription of the *RAD51* gene [24]. This polymorphism was associated with decreased DNA damage detected with comet assay in healthy individuals [21] and lower amount of gamma radiation-induced chromatid breaks [24], suggesting a protective effect.

3.3. *XRCC3*

XRCC3 is one of XRCC proteins involved in the protection of cell from ionizing radiation and belongs to the RAD51 family [25]. XRCC3 deficiency affects RAD51 foci formation and leads to increased genetic instability and sensitivity to DNA damaging agents [26].

Only a few putatively functional SNPs have been described in the *XRCC3* gene. Among them, non-synonymous polymorphism rs861539 (p.Thr241Met) and rs1799794 (c.-316A>G) polymorphism in 5′ UTR were the most frequently studied. *XRCC3* rs861539 changes the amino acid residue, which could affect protein structure or function [12]. Polymorphic rs861539 allele was previously associated with decreased DNA damage detected with comet assay in healthy individuals [21] and had a protective effect against chromosomal aberrations [27], but not in all studies [28].

3.4. *XRCC2*

XRCC2 is also one of the RAD51 paralogs, necessary for successful HRR. It is essential in the early stages of HRR for the formation of RAD51 foci, but it does not require ATP binding [29].

Studies have shown that XRCC2 deficiency leads to defects in RAD51 foci formation, markedly decreased HRR and increased DNA damage, as well as hypersensitivity to radiation [29-31].

Among SNPs that have been described in *XRCC2*, the only non-synonymous rs3218536 (p.Arg188His) polymorphism attracted the most attention, despite its relatively low MAF and very few individuals carrying two polymorphic alleles. A deletion or a non-conservative substitution in the position 188 markedly increased sensitivity to mitomycin C induced DNA damage, but the common Arg188His substitution only had a small influence on damage sensitivity [32]. As the variant *XRCC2* 188His allele was associated with increased resistance to cisplatin induced DNA damage, it was suggested that it could be associated with increased DNA repair capacity [13]. The observed differences could be partly due to the use of different DNA damaging agents. It was suggested that lesions caused by different agents could require more precise regulation of protein expression to reach full repair potential [13].

4. Genetic variability in HRR and cancer susceptibility

Due to important role of DSBs in carcinogenesis, several studies have investigated the role of HRR SNPs in cancer susceptibility. To overcome the problem of non-concordant effects observed in some studies, several meta-analyses have been performed. Meta-analyses have the advantage of larger sample sizes and better statistical power. Their results suggested that HRR SNPs may contribute to cancer susceptibility, but their role may not be the same in all cancer types or in all populations, especially as MAFs can differ substantially for some polymorphisms. Another shortcoming of the meta analyses is that gene-gene and gene-environmental interactions could modify the role of SNPs, but the results of meta-analyses are usually not adjusted for confounders. In addition, it is difficult to perform meta-analyses in rare cancers.

4.1. *NBN*

Genetic variability in *NBN* was associated with susceptibility to different hematological and solid tumors. Several meta-analyses have been published to date, showing that *NBN* mutations and polymorphisms may have different effects in different cancer types (Table 3).

Mutation / SNP	Reference	N of studies	N of cases/controls	Cancer type	Major observation*
Ile171Val	Bogdanova, 2008 [33]	4	2954/2531	Breast	No association
	Gao, 2013 [4]	10	4516/9951	Overall	Increased risk
		5	3301/3904	Breast	No association
		2	182/720	Lymphoma	Increased risk
	Zhang, 2012 [34]	5	3273/4004	Breast	No association
Arg215Trp	Gao, 2013 [4]	9	6728/9508	Overall	Increased risk
657del5	Zhang, 2012 [34]	9	7534/14034	Breast	Increased risk

Mutation / SNP	Reference	N of studies	N of cases/controls	Cancer type	Major observation*
	Zhang, 2013 [35]	10	25365	Breast	Increased risk
	Gao, 2013 [4]	21	15184/54081	Overall	Increased risk
		10	9091/15154	Breast	Increased risk
		5	1053/9524	Lymphoma	Increased risk
		2	3440/2490	Prostate	Increased risk
rs1805794	Vineis, 2009 [36]	4	∑4825	Bladder	Increased risk
	Lu, 2009 [37]	17	9734/10325	Overall	Borderline increased risk
		6	4595/3603	Breast	No association
		3	605/639	Lung	No association
		3	1446/1452	Bladder	No association
	Stern, 2009 [38]	13	6348/6752	Bladder	Modestly increased risk
	Wang, 2010 [39]	10	4452/5665	Breast	Decreased risk Not credible, some mistakes [40]
	Wang, 2013 [41]	6	2348/2401	Lung	Increased risk
	Yao, 2013 [42]	14	6642/7138	Breast	No association
	He, 2014 [43]	48	17159/22002	Overall	No association
		7	2837/2973	Urinary system	Increased risk
		5	1682/2213	Digestive system	Decreased risk
	Zhang, 2014 [44]	8	3542/4210	Urinary system cancer	Increased risk, especially in bladder cancer
	Gao, 2013 [4]	42	18901/21430		No association in subgroup analysis by cancer type, heterogeneity too big for overall analysis
rs2735383	Gao, 2013 [4]	13	7561/8432	Overall	Increased risk
		4	2915/3035	Lung	Increased risk
rs1063054	Gao, 2013 [4]	9	2757/5796	Overall	Increased risk

*the direction of association for the mutated or polymorphic allele; ∑ - the total number of cases and controls

Table 3. Observed influence of *NBN* genetic variability on cancer risk in meta-analyses.

Rare mutations in the *NBN* gene have a more deleterious effect on the gene function and therefore have a bigger influence on cancer risk [4]. Even though the results of individual studies differed, several meta-analyses observed similar influence of various *NBN* mutations

on cancer risk (Table 3). *NBN* 657del5 mutation was associated with increased overall cancer risk, as well as increased risk for breast cancer, prostate cancer, and lymphoma [4, 34, 35]. Interestingly, Ile171Val mutation did not predispose to increased breast cancer risk [4, 33, 34], but it was associated with overall increased risk of cancer and increased lymphoma risk [4]. The results of the meta-analysis showed that Arg215Trp mutation also significantly increased the overall cancer risk, in contrast with Asp95Asn and Pro266Leu mutations that were not associated with increased cancer risk [4].

Most of the meta-analyses investigating the role of *NBN* polymorphisms in cancer susceptibility were limited to the non-synonymous rs1805794 SNP (Table 3). Most studies have confirmed that polymorphic allele modestly increases bladder cancer risk [36, 38, 43]. The results in other cancer types were more ambiguous as some studies observed an association with increased cancer risk, but several did not (Table 3). Interestingly, in one meta-analysis decreased risk was observed for cancers of digestive system [43]. Decreased risk was also reported in some studies in rare cancer types such as acute myeloid leukemia [45] or osteosarcoma [46]. The observed discrepancies could be due to large heterogeneity between studies. Also *NBN* genotype distribution differs among populations, as the variant rs1805794 C allele is more common in some populations [21, 47]. Therefore it is not surprising that meta-analyses observed significant influence of *NBN* SNPs only in specific subgroups: only in Caucasians [37], only in Asians [41], or only among smokers [38]. Further studies should pay special attention to these differences as they could help explain discrepancies among studies. As the effect of a particular SNP may differ among cancer types, analyses should be stratified by cancer type. However, this can present a problem in rare cancer types, as it may be difficult to achieve sufficient power.

Among other *NBN* SNPs, one meta-analysis included two SNPs in the 3' UTR, rs2735383 and rs1063054. The results suggested that both SNPs contribute to increased overall cancer risk [4]. However, when the analysis was stratified by cancer type, rs2735383 was only associated with increased lung cancer risk, but no significant association with bladder, nasopharyngeal cancer or leukemia was observed. *NBN* rs709816 was not associated with modified cancer risk in any of the studies [17].

4.2. *RAD51*

RAD51 rs1801320 is the most studied polymorphism in this gene despite its relatively low MAF. Several meta-analyses were published on the influence of rs1801320 on breast cancer risk until 2011, but they were mostly inconclusive [48-52]. Several shortcomings in the analyses associated with data and inclusion of these studies were later noted [53], suggesting that many of these studies were unreliable. More recent meta-analyses are presented in Table 4. Some suggested that rs1801320 may increase breast cancer susceptibility [54, 55], but one of the studies suggested a potential role of this polymorphism only in individuals with *BRCA2* mutations [56]. BRCA2 directly interacts with RAD51 and influences intracellular transport as well as function of RAD51 [57], thus playing an important role in HRR, so these observations are biologically plausible.

RAD51 rs1801320 SNP was also associated with increased overall cancer risk in the two largest meta-analyses that included more than 40 individual studies [54, 55], however no association was observed in an earlier study [56]. Increased risk for several cancer types, including hematological malignancies, ovarian, colorectal, and endometrial cancer was observed in a recent study [55], but not all were replicated in other studies (Table 4).

Another *RAD51* polymorphism, rs1801321 was investigated in only one meta-analysis and even though overall cancer risk was not modified [54], the decreased risk in carriers of polymorphic allele for head and neck cancer confirmed the results of previous studies [24]. Decreased breast cancer risk was also observed in carriers of polymorphic allele [58]. The suggested protective role of rs1801321 is in concordance with the described biological effect of this polymorphism.

Reference	N of studies	N of cases/controls	Cancer type	Major observation*
He, 2014 [59]	10	2656/3725	Myelodysplastic syndrome and acute leukemia	No association
	3	726/604	Myelodysplastic syndrome	Increased risk
Wang, 2013 [56]	39	19068/22630	Overall	No association
	7	1605/3121	Acute myeloid leukemia	No association
	14	11709/11291	Breast	No association
	6	2388/4411	Ovarian	No association
Cheng, 2014 [60]	22	6836/8507	Overall	No association
	4	1237/1340	Squamous cell carcinoma of the head and neck	Increased risk
	4	753/720	Colorectal	No association
	5	2001/2420	Ovarian	No association
	9	2845/4027	Acute leukemia	No association
Zhao, 2014 [54]	42	19142/20363	Overall	Increased risk
	17	11716/9839	Breast	Increased risk
Shi, 2014 [61]	10	2648/4369	Ovarian	No association
Li, 2014 [62]	6	1764/3469	Acute myeloid leukemia	No association
Zhang, 2014 [55]	45	28956/28372	Overall	Increased risk
	19	19171/17198	Breast	Increased risk
	7	2169/3629	Hematological malignancies	Increased risk
	4	3598/3002	Ovarian	Increased risk
	4	1202/1216	Head and neck	No association

*the direction of association for the polymorphic allele

Table 4. Observed influence of *RAD51* rs1801320 on cancer risk in meta-analyses.

4.3. *XRCC3*

XRCC3 is by far the most studied HRR gene in cancer susceptibility studies. More than 50 meta-analyses focusing on *XRCC3* rs861539 SNP have been published, so only recent studies published in 2014 are presented in Table 5. The polymorphic rs861539 allele was associated mostly with increased breast and bladder cancer risk, but decreased lung or skin cancer risk [63-65]. An interesting observation is almost consistently observed increased cancer risk in carriers of polymorphic allele from Asian populations, while usually no association was observed in Caucasian populations or when different populations were combined.

Reference	N of studies	N of cases/controls	Cancer type	Major observation*
Mao, 2014 [66]	36	23812/25349	Breast	Slightly increased risk, especially in Asians
Xing, 2014 [67]	8	3215/3106	Lung	No association
Yuan, 2014 [12]	4	5173/7800	Ovarian	No association
Feng, 2014 [68]	8	3455/4435	Glioma	No association
Li, 2014 [69]	5	1507/3623	Larynx	No association
Adel Fahmideh, 2014 [70]	5	3374/3734	Glioma	No association
Chen, 2014 [26]	15	4329/7291	Overall	No association
	8	2056/3920	Non-melanoma skin cancer	Decreased risk
	5	1324/2209	Basal cell carcinoma	Decreased risk
	3	732/1711	Squamous cell carcinoma	Decreased risk
Qin, 2014 [71]	9	2209/3269	Gastric	No overall, association, increased risk in Asians
Yu, 2014 [72]	6	723/1399	Thyroid	No overall association, increased risk in Caucasians
Yan, 2014 [73]	7	1070/1850	Leukemia	No overall association, increased risk in Asians
Yan, 2014 [74]	7	3635/5473	Ovarian	No association
Qin, 2014 [75]	15	2339/4162	Leukemia	No overall association, increased risk in acute myeloid leukemia

Reference	N of studies	N of cases/controls	Cancer type	Major observation*
Wang, 2014 [76]	12	2209/3269	Gastric	No overall association, decreased risk in Asians
Du, 2014 [77]	23	7777/9868	Overall (Chinese mainland population)	Increased risk, especially cervical and nasopharyngeal cancer
Wang, 2014 [78]	10	4136/5233	Glioma	No overall association, increased risk in Asians
Liu, 2014 [79]	13	4984/7472	Brain tumors	No overall association, increased risk in Asians
Ma, 2014 [80]	18	5667/7609	Bladder	Increased risk
Peng, 2014 [81]	16	5608/6197	Bladder	Increased risk

*the direction of association for the polymorphic allele

Table 5. Observed influence of *XRCC3* rs861539 on cancer risk in recent meta-analyses.

Only a few meta-analyses were performed for *XRCC3* rs1799794. This polymorphism in 5'UTR was associated with increased overall and breast cancer risk in earlier studies [64, 82], but the association with breast cancer was not confirmed [83] and a decreased ovarian cancer risk was observed in a more recent meta-analysis [12].

4.4. *XRCC2*

The majority of cancer susceptibility studies focused solely on the *XRCC2* rs3218536 SNP. Different types of cancer were investigated, but most studies were performed in breast and ovarian cancer. Recent meta-analyses summarized in Table 6 tried to overcome the discrepancies observed between individual studies [61, 84-86]. All meta-analyses observed an association of the polymorphic rs3218536 allele with decreased ovarian cancer risk [61, 84, 86]. On the other hand, no association with breast cancer risk was observed in the most recent meta-analyses [61, 84, 86], confirming the results of a previous meta-analysis [85]. Although overall cancer risk was also not significantly affected by *XRCC2* rs3218536 [86], it was suggested that different cancer types should be evaluated separately [84]. However, a conclusive role of *XRCC2* rs3218536 in other cancer types is still difficult to ascertain, due to the limited number of studies investigating a particular cancer. Nevertheless, polymorphic *XRCC2* rs3218536 could be associated with increased risk for cancer of upper aerodigestive tract [84].

Apart from separate evaluation of different cancer types, further studies should investigate the possible interactions that could modify the role of XRCC2 SNPs. Several studies on breast cancer reported an association only in specific subgroups of patients, suggesting that besides genetic variability, also environmental factors and gene-environment interactions could

contribute to cancer risk. Such interactions could also help to explain the effect of low penetrance variants on cancer risk.

Reference	N of studies	N of cases/controls	Cancer type	Major observation*
Yu, 2010 [85]	16	18341/19028	Breast	No association
He, 2014 [84]	14	17420/17811	Breast	No association
	6	3035/5554	Ovarian	Decreased risk
	3	499/583	Upper aerodigestive tract	Increased risk
Shi, 2014 [61]	9	3279/5934	Ovarian	Decreased risk
Zhang, 2014 [86]	33	26320/28862	Overall	No association
	12	17230/16485	Breast	No association
	6	3035/5554	Ovarian	Decreased risk

*the direction of association for the polymorphic allele

Table 6. Observed influence of *XRCC2* rs3218536 on cancer risk in meta-analyses.

5. Genetic variability in HRR and cancer treatment outcome

Cancer treatment is often associated with severe adverse effects, however there is considerable interindividual variability regarding the occurrence and severity of adverse effects and regarding treatment efficacy. As cancer treatment is usually based on the use of chemotherapeutic agents and radiation therapy, whose cytotoxic effect results from their ability to induce DNA damage, pharmacogenetic factors such as polymorphisms in DNA repair pathways can contribute to observed differences.

Different agents may cause different forms of DNA damage. DSBs can occur due to the formation of strand crosslinks after treatment with alkylating and platinum-based compounds. Mechanisms involved in DSB repair may also lead to increased sensitivity to topoisomerase inhibitors such as camptothecines, anthracycline, and etoposide. DSB repair may be also important for the repair of radiation-induced DNA damage. Genetic variability of HRR may thus play a role in resistance to chemotherapy, in treatment efficacy and in occurrence of treatment related toxicities.

There are a lot less pharmacogenetic studies investigating the role of genetic variability in HRR in cancer treatment outcome compared to studies on cancer susceptibility. In addition, many studies are small and/or inconclusive and the shortcoming of most of the studies is that DNA repair capacity itself was not measured. Most pharmacogenetic studies focused on *XRCC3* polymorphisms and were predominantly investigating their influence on treatment with platinum compounds. *XRCC3* rs861539 was associated with shorter survival in ovarian and colorectal cancer [87, 88]. Most studies were however performed in non-small cell lung cancer

(NSCLC), where *XRCC3* rs861539 was associated with better response rate. Even though this effect was not observed in all the studies, recent meta-analyses confirmed the possible prognostic value of *XRCC3* rs861539 in response to cisplatin-based chemotherapy in NSCLC patients (Table 7). Although individual studies observed the association of this SNP with longer overall survival of NSCLC patients [89, 90], that was not confirmed in meta-analyses [91-93]. Several studies also observed an association of *XRCC3* rs861539 with decreased toxicity of platinum compounds in malignant mesothelioma, colorectal cancer and other malignancies [94, 95]. *XRCC3* rs1799794 was also associated with decreased odds of developing treatment related toxicities in malignant mesothelioma [95]. Some of the discrepancies observed between studies could be explained by different chemotherapy regimens used in different cancer types.

Reference	N of studies	N of cases	Major observation*
Shen, 2013 [92]	7	1186	Better response to chemotherapy, no significant influence on overall survival
Qiu, 2013 [91]	8	1289	Better response to chemotherapy, no significant influence on overall survival
Zhang, 2013 [93]	7	1514	No significant influence on overall survival

*the direction of association for the polymorphic allele

Table 7. Meta-analyses of *XRCC3* rs861539 and treatment outcome in non-small cell lung cancer.

The role of genetic variability in other HRR genes in cancer treatment outcome is currently not well established. Pharmacogenetic studies of other HRR genes were limited to individual studies in particular cancer types. *NBN* polymorphisms have been associated with increased treatment-related toxicity of gemcitabine-platinum combination chemotherapy in patients with malignant mesothelioma [95]. On the other hand, *NBN* rs1805794 was associated with longer progression-free survival in NSCLC patients treated with platinum-based chemotherapy, suggesting it might serve as a favourable prognostic factor [96].

RAD51 rs1801320 and rs1801321 polymorphisms were also associated with altered survival in NSCLC and cervical cancer patients [97-99], but no prognostic role was observed in malignant mesothelioma or sarcoma patients [95, 100].

Similar to other HRR genes, the potential influence of *XRCC2* on cancer treatment outcome was not studied as often as cancer risk. The low MAF of *XRCC2* rs3218536 could be a part of the reason why there is a lack of studies regarding treatment outcome. *XRCC2* rs3218536 was associated with decreased survival in pancreatic cancer and NSCLC patients [99, 101], but the association was significant only in specific subgroups of patients. In pancreatic cancer patients, treated with chemotherapy and radiation, the polymorphic *XRCC2* rs3218536 allele was associated with decreased survival only in patients treated with 5-fluorouracil based chemoradiation, but not in patients treated with gemcitabine based chemoradiation [101]. These

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differences further support observations that the effect of HRR polymorphisms may depend on the type of DNA damage.

Radiation therapy is used for treatment of up to 50% of cancer patients [102]. Adverse events are common and affect patients' quality of life [103]. They occur mainly locally in irradiated sites and therefore vary between cancer types. Acute toxicities affect rapidly proliferating tissues, but are usually transient and reversible [102]. Erythema and dermatitis are common skin acute adverse events, radiation pneumonitis is a typical complication in lung cancer, while urinary and bowel toxicities occur in prostate cancer.

The new field of radiogenomics aims to identify SNPs associated with radiation toxicity that could be used for personalized radiation therapy of cancer patients, for example patients with low risk for adverse events could receive higher doses of radiation [103]. As DSBs represent the most harmful effect of radiation, several studies have been published regarding HRR SNPs and radiation toxicity.

NBN polymorphisms did not influence toxicity in prostate, breast or lung cancer [99, 104, 105], but *NBN* rs1805794 was associated with oral mucositis in head and neck cancer patients treated with radiation or chemoradiation [106]. *RAD51* rs1801320 was also associated with toxicity in head and neck cancer in one study [107], as well as radiation pneumonitis in lung cancer patients [99]. Other studies did not report any association of *RAD51* SNPs and radiation toxicity [104, 108-110]. *XRCC2* rs3218536 was not associated with radiation toxicity in any of the studies [99, 104, 111]. Numerous studies investigated the role of *XRCC3* poymorphisms in radiation toxicity, but the results are not conclusive. Several studies found no association [99, 105-107, 109, 111-113], but carriers of polymorphic *XRCC3* rs1799794 allele had more toxicity after radiation treatment of prostate cancer [104, 114] and *XRCC3* rs861539 was associated with increased radiation toxicity in nasopharyngeal cancer [115, 116].

Comparison of radiogenomics studies is difficult, as they were performed in different cancer types treated with different radiation therapy protocols, sometimes in combination with chemotherapy. Additionally, different toxicities were selected as endpoints. Nevertheless, the published data suggest the impact of some of the HRR polymorphisms on the outcomes of radiation therapy, however meta-analyses are needed to validate these observations.

6. Conclusions

The combined evidence from different studies and meta-analyses suggests that SNPs in HRR genes contribute to carcinogenesis and could serve as markers of cancer susceptibility. As HRR proteins often interact in DNA repair, future studies should evaluate if combinations of SNPs in different HRR genes may serve as a better predictor of susceptibility to various cancers.

Cancer treatments are often characterized by a narrow therapeutic index and a balance between the desired therapeutic effect and the acceptable treatment-related toxicity has to be achieved. In the future, the improved understanding of the role of HRR genetic variability in the response to treatment of a particular cancer with a particular chemotherapeutic regimen

could contribute to identification of predictive or prognostic biomarkers that could help to stratify patients based on their risk for adverse events and guide treatment selection. Thus, treatment from which a particular patient would benefit the most could be selected.

In conclusion, genetic variability in HRR may modify DNA repair capacity and may therefore play an important role in both cancer susceptibility and the outcome of cancer treatment. A better understanding of the role of SNPs in HRR genes in different cancers and cancer treatments is however needed before they could be employed as markers of cancer susceptibility or treatment outcome in personalized medicine.

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