The RAD51 gene family, genetic instability and cancer.

John Thacker
Medical Research Council, Radiation & Genome Stability Unit, Harwell, Oxfordshire OX11 0RD, England.

Tel 01235-841000
Fax 01235-841200
e-mail j.thacker@har.mrc.ac.uk

Key words: homologous recombination / genetic instability / RAD51 / XRCC2 / XRCC3 / RAD51L1 (RAD51B) / RAD51L2 (RAD51C) / RAD51L3 (RAD51D) / breast cancer

Abstract
Inefficient repair or mis-repair of DNA damage can cause genetic instability, and defects in some DNA repair genes are associated with rare human cancer-prone disorders. In the last few years, homologous recombination has been found to be a key pathway in human cells for the repair of severe DNA damage such as double-strand breaks. The *RAD51* family of genes, including *RAD51* and the five *RAD51*-like genes (*XRCC2, XRCC3, RAD51L1, RAD51L2, RAD51L3*) are known to have crucial non-redundant roles in this pathway. Current knowledge of the functions of the *RAD51* gene family is reviewed, as well as the evidence for extensive genetic instability arising from loss of their activity. Reports of potential associations between variants of *RAD51* family genes and specific forms of cancer are summarised, but it is seen that many of these studies have relatively low statistical power. As yet these data provide only tantalizing suggestions of modified cancer risks arising from polymorphisms, mutations, or changes in expression of the RAD51 gene family, and there is still a lot to learn before firm conclusions can be made.

1. Introduction

It is well established that germline mutations in DNA damage-response genes are linked to cancer susceptibility in humans and animal models. Well-characterized human examples of defective DNA repair processes associated with cancer predisposition include DNA mismatch repair with colorectal cancer, nucleotide excision repair with skin cancer, and homologous recombination repair with breast and ovarian cancer [1,2]. A less well-established, but prevalent, idea is that genetic instability created by sporadic loss of damage-response mechanisms is important in cancer initiation and/or progression. This suggestion has led to much debate over the driving forces involved in cancer development (for contrasting views see: [3-5]). However, it is not doubted that tumours carry large numbers of genetic alterations (e.g., [6]), and that a succession of genetic changes is usually required to achieve the mature cancer [7]. Therefore there is considerable interest in the cellular mechanisms that can lead to genetic change, and in particular to genetic instability.

2. DNA repair by homologous recombination

Several different repair pathways have evolved to cope with DNA damage from both endogenous (e.g., oxidative radicals) and exogenous sources (e.g., radiation, chemicals). Although characterized initially in micro-organisms, in the last few years it has been found that repair of damage by homologous recombination (HR) is a key pathway in somatic mammalian cells. HR is particularly important during and following DNA replication, when a sister DNA molecule (chromatid) is present as a template for repair. In eukaryotes the central HR protein is RAD51 which catalyses strand transfer between a broken sequence and its undamaged homologue to allow re-synthesis of the damaged region [8]. Unexpectedly, through the cloning of damage-response genes and sequence-similarity searches, five further genes encoding RAD51-like proteins were found in human cells (a sixth RAD51-like protein, named DMC1, functions only in meiosis). These proteins were called XRCC2, XRCC3 (XRCC = ability to complement X-ray sensitivity), RAD51L1 (RAD51B), RAD51L2 (RAD51C) and RAD51L3 (RAD51D) [review: 9]. The regions of highest sequence conservation among these proteins is found in the putative ATP-binding domains [10,11], and conservation elsewhere is limited (note that while these proteins are commonly termed RAD51 'paralogues', this term should be reserved for proteins known to be derived from a single gene that was duplicated within a genome [12]). At the time of their discovery very little was known about the functions of these proteins, but a combination of biochemical, cellular and animal studies has revealed some important and sometimes surprising attributes.

3. The RAD51 family: roles in early and late stages of HR?

As noted above, RAD51 itself has the core function of strand invasion: that is, polymerizing onto a 3' DNA end and mediating the transfer and annealing of the resulting nucleoprotein filament to a complementary homologous strand on the intact chromatid. This invasion displaces the non-complementary intact strand, forming a 'D-loop' which enlarges as new DNA synthesis progresses across the break site. Finally enzymatic resolution of the cross-stranded structure (Holliday junction) must occur (Fig.1). In addition to these intricate steps, the HR process has to overcome internal DNA bonding forces to unwind and separate DNA strands, as well as competing with other DNA binding proteins. These complexities predict a requirement for a number of other specialized proteins in addition to the 5 RAD51-like proteins, to complete the task. Relevant proteins include RAD52 and RAD54, although in neither case is their function fully understood, as well as the breast-cancer predisposition proteins BRCA1 and BRCA2 [13]. Recent structural studies suggest a mechanism for the regulation of RAD51 activity by BRCA2, and cancer-associated mutations affecting the domain where RAD51 binds to BRCA2 disrupt this interaction [14]. Although the RAD51-like proteins have overall homology to RAD51, structural studies suggest that they have diverged sufficiently so that they would not bind BRCA2 at this domain [15].

In the search for the role of the RAD51-like proteins, 2-hybrid interactions [16] and protein co-immunoprecipitation indicated that the RAD51-like proteins form heterodimers: XRCC2 with RAD51L3 [17], RAD51L1 with RAD51L2 [18,19], and XRCC3 with RAD51L2 [20-22]. It is noteworthy that RAD51L2 is involved in two different heterodimers, and that subsequent studies showed the existence of a heterotetrameric complex of RAD51L1/RAD51L2/RAD51L3/XRCC2 in an approximately 1:1:1:1 stochiometry [19,23,24].

Fig.1 Homologous recombination repair of a DNA double-strand break (simplified). The HR process is shown in several stages, with attendant proteins (in reality these steps will be integrated and the proteins may function at more than one stage). 3' single-stranded tails formed by resection of break

ends are coated with RAD51 following displacement of single-stranded binding protein (RPA) probably with the assistance of RAD52 (with strand-annealing activity) and the RAD51-like protein heterotetramer (see text). A 3' end (grey molecule) invades an unbroken (black) molecule, displacing a strand (D-loop) that acts as a repair template. RAD54 appears to have both pre- and post-invasion roles, to facilitate the opening up of DNA and perhaps the removal of proteins by translocation along DNA. Following repair synthesis and strand migration, recent data suggest that the cross-stranded structures formed are resolved by the XRCC3/RAD51L2 heterodimer (see text).

What do these RAD51-like protein complexes do? Most of the RAD51-like proteins have been shown to have DNA-stimulated ATPase activity and preferentially bind single-stranded DNA [17,18,20,23,25]. However, where mutant cell lines were available to test function of the proteins, site-directed mutagenesis of key residues in the ATP-binding domain showed that for one protein (XRCC2) function is unaffected [26], while for another (RAD51L2) function is severely reduced [27]. It might have been expected that some or all of these complexes interact with RAD51, but the evidence to date suggests that any interactions are relatively weak or not stable [16,19,22-25]. This is curious since it has been shown that XRCC3 [28], XRCC2 [26] and RAD51L2 [29,30] are required for formation of induced RAD51 foci (accumulation of RAD51 protein at sites of DNA damage) in cell nuclei.

In vitro reactions that attempt to mimic the RAD51-mediated strand transfer/displacement process – using linear single-stranded (ss) and circular double-stranded (ds) DNA with purified proteins - suggested that both XRCC3/RAD51L2 [21] and XRCC2/RAD51L3 [31] complexes catalyze DNA strand pairing and displacement activity. In contrast, using similar methods, strand transfer/displacement activity by XRCC3/RAD51L2 was not found [20]. However, when ss-DNA binding protein (RPA) was present in a reaction between ss circular and ds linear DNA, the presence of the RAD51L1/RAD51L2 complex was found to improve RAD51-mediated strand exchange [18]. Further, in reactions between ss and ds oligonuclotides, RAD51L2 but not RAD51L1, was shown to have DNA melting and strand-separation activity rather than strand exchange activity [25]. While some of these data suggest therefore that at least RAD51L2 has activity at an early recombination step, they also show that the in vitro modelling of recombination reactions has some way to go to reproduce in vivo conditions.

In addition to these data on early steps of HR processing (Fig.1), there is new evidence that the RAD51-like proteins may also act at later stages. Analysis of proteins present in purified fractions and measurement of Holliday junction (HJ) resolvase activity in radiosensitive cell lines suggested that the XRCC3/RAD51L2 heterodimer is required for HJ resolution [32]. Indirect support for this finding comes from some other recent data: recombination in XRCC3-deficient cells was found to be more commonly associated with rearrangements, and the recombined sequence tract was longer and more discontinuous, when compared to cells expressing XRCC3 [33]. Additionally, based on the phenotype of RAD51L2-deficient cells, a model for the involvement of this protein in maintaining the integrity of recombination intermediates at the stage of resolving HJ was proposed [29].

4. Does the RAD51 family ensure genetic stability?

Early studies, undertaken before the genes were cloned, showed that the frequency of genetic changes was increased in cells lacking XRCC2 and XRCC3 [review: 10], but it is only recently that extensive studies of genetic stability have been published. Knocking out RAD51 in mice gave very early embryonic lethality [34,35], while knockouts of XRCC2 [36], RAD51L1 [37] and RAD51L3 [38] allowed the embryos

to progress until later but no live births were found. Loss of RAD51 also did not allow cell cultures to be established even in a p53-deficient background [34], and switching off *RAD51* gene expression in chick DT40 cells led to the accumulation of cells in G2/M with large amounts of chromosomal breakage [39]. Overexpression of *RAD51* in cells can stimulate HR [40-43] or reduce HR [44], but can potentially lead to chromosome rearrangements [45]. However, injection of cells overexpressing *RAD51* into nude mice did not result in an increased tumour burden, while cells carrying dominant-negative *RAD51* constructs (i.e., mutant forms of the gene inhibiting HR activity) increased tumorigenesis two-fold [46].

In a recent detailed study of MEFs and ES cells derived from the *XRCC2* knockout mouse, high frequencies of chromosomal instability, with especially high frequencies of chromosome exchange and aneuploidy were found ([47] and C.S. Griffin & J. Thacker, submitted). Additionally, MEFs heterozygous for the *Xrcc2* knockout showed increased chromosome aberrations and centrosome fragmentation, suggesting mild haploinsufficiency. XRCC2- and XRCC3-deficient hamster cells have been shown to have increased mis-segregation of chromosomes resulting in aneuploidy, and the centrosome defect was suggested to be linked to this phenotype [48,49]. Very recently, a role for RAD51L3 in chromosome telomere maintenance has been proposed, and part of this study showed that mouse cells deficient in both RAD51L3 and p53 have an increased frequency of chromosome aberrations including a small increase in telomeric end-to-end fusions [50].

It is relevant to note also that loss of the breast cancer-predisposing genes *BRCA1* and *BRCA2* leads high levels of chromosomal instability [51,52], as well as to centrosome defects and aneuploidy [53,54]. It is clear therefore that generally the loss of genes associated with *RAD51* leads to multiple forms of genetic instability. In particular, the chromosomal segregation defect has not been found for cells deficient in alternative repair pathways such as simple end-joining of DNA breaks [48,55], and may have far-reaching consequences, since aneuploidy is commonly associated with cancer [5].

5. The cancer connection

There are sufficient indications from the above overview to suggest that activities of the *RAD51* gene family may influence carcinogenesis, especially in view of the links between *RAD51* and the *BRCA* genes.

To assess the impact of repair gene activity on carcinogenesis, several different approaches have been used. An important source of potential genetic variants occurs in naturally-occurring polymorphisms in the human genome. The sequencing of repair genes from normal individuals has shown that, for each gene, several different amino acid substitution variants occur, although most of these are found in less than 2% of individuals [56]. Predictions of the impact of these variants have been made using different algorithms, suggesting that >30% would be potentially damaging due to reduced activity [57]. Studies attempting to implicate some of the *RAD51* family variants in the modification of cancer risk are listed in Table 1. The potential for harm of a given variant is mostly shown by an odds ratio: the odds of an event are calculated as the number of events in the study group divided by the number of events in the control group (and statistically significant odds ratios should not include 1.0 in their 95% confidence intervals).

Table 1 Potential associations between *RAD51* family sequence variants and cancer

Gene/ protein	Variant[1]	Cancer type	Risk association[2]	Ref.
RAD51	G135C (5' UTR). Frequency 0.05-0.26	Breast cancer in *BRCA1* and *BRCA2* carriers	Increase (both genes: OR 1.6, CI 1.0-3.4; *BRCA2*: OR 3.2, CI 1.4-40)	[86]
		Breast cancer in *BRCA1* and *BRCA2* carriers	Increase for *BRCA2* (*BRCA1*: OR 1.2, ns; *BRCA2*: OR 3.5, 1.4-8.9)	[87]
		Breast cancer in *BRCA1* and *BRCA2* carriers	Increase for *BRCA2* (both genes: OR 1.3, CI 0.9-1.9; *BRCA2* OR 2.1, CI 1.0-4.2)	[88]
		Breast cancer in *BRCA1* carriers	Decrease (OR 0.23, CI 0.1–0.6)	[89]
XRCC2	G31479A (Arg188His). Frequency 0.01-0.07	Breast cancer	Marginal increase for all carriers (OR 1.3, CI 1.0-1.8) but ns for homozygous variant (OR 2.1, CI 0.7-7.1)	[58]
		Breast cancer	Marginal increase for homozygous variant (OR 2.6, CI 1.0-6.7), ns for heterozygote variant	[90]
		Breast cancer	Increase (at low plasma folate levels only; OR 2.04; CI 1.1-4.0); Overall ns 1.1 (0.9–1.4)	[91,92]
		Skin cancer	No effect for melanoma, squamous cell carcinoma or basal cell carcinoma	[93]
	G30833A (3' UTR). Freq. 0.10	Basal cell carcinoma[3]	Increase (OR 1.7 CI 1.1-2.7)	[93]
XRCC3	A4552C (5' UTR) Freq. 0.18	Basal cell carcinoma	Increase for homozygous variant (OR 2.2 CI 1.2-4.2)	[93]
	A4541G (5'-UTR) Freq. 0.19	Breast cancer	ns effect 1.2 (1.0–1.4)	[92]
	A17893G (IVS5-14) Freq. 0.31	Breast cancer	No effect 1.0 (0.9–1.3)	
	C18067T (Thr241Met). Frequency 0.07-0.45	Malignant melanoma	Increase (OR 2.36, CI 1.4–3.9)	[94]
		Bladder cancer	Increase in carriers with NAT-2 slow genotype (OR 3.4, CI 1.5-7.9)	[95]
		Lung cancer	No effect (OR 0.95, CI 0.7–1.3)	[96]
		Malignant melanoma	No effect (OR 0.94, CI 0.7–1.3)	[97]
		Bladder cancer	ns effect (OR 1.3, CI 0.9-1.9)	[98]
		Squamous cell carcinoma of the head and neck	ns effect overall (OR 1.4, CI 0.9-2.1); marginal increase for females (OR 2.2, CI 1.0-5.0) and smokers (OR 2.3, CI, 1.0-5.0)	[99]
		Breast cancer	No effect (OR 0.9, CI 0.5-1.5)	[100]
		Lung cancer	No overall effect (OR 1.3, CI 0.7-2.2) but increase for heavy smokers (OR 5.2, CI 1.6-17.0)	[101]
		Basal cell carcinoma Lung cancer	No effect Homozygote OR 0.9 (0.5–1.4) No effect Homozygote OR 0.9 (0.6–1.4)	[102]
		Malignant melanoma	No effect	[103]

		Basal cell carcinoma[3]	Decrease for all carriers (OR 0.7 CI 0.5-0.9) and homozygous variant (OR 0.6 CI 0.4-0.9)	[93]
		Breast cancer	No effect 0.9 (0.8–1.1)	[92]
		Breast cancer	Marginal increase for homozygote (OR 1.4, CI 0.9-2.2) but not for heterozygote (OR 1.0, CI 0.7-1.3)	[104]
RAD51L3 (RAD51D)	Glu233Gly Freq. 0.02	Breast cancer	Increase (OR 2.6, CI 1.1-6.0)	[61]

[1] Position and change (right-hand base) in DNA sequence, but note that nucleotide numbering will vary depending on the reference sequence. If the variant is in coding sequence, the protein position/change is also shown in parenthesis. The range of variant frequency in different groups of normal individuals is also shown where known.
[2] Data are given for individuals carrying at least one variant allele, unless otherwise stated. ns = non-significant; OR = odds ratio (measure of relative risk, where a value of 1.0 shows no alteration of risk); CI 95% confidence interval.
[3] no significant change for melanoma or squamous cell carcinoma for *XRCC2* G30833A or *XRCC3* C18067T; and no increase for other variants for any skin cancer.

It should be noted that many of these studies have examined relatively small numbers of patients, leading to low statistical power with attendant possibilities of false positives and negatives. However, overall these data suggest the following:

- *BRCA2* mutation carriers (but not *BRCA1* mutation carriers) are at greater risk of breast cancer when also carrying the *RAD51* variant G135C.
- *XRCC2* codon 188 variant may carry a small increased risk of breast cancer. While this codon is important for gene function as shown by deletion or mutation to a non-conservative amino acid (measured by resistance to DNA damage), the Arg188His variant has only marginal effects on gene function [58].
- The early report of an association between *XRCC3* codon 241 variant and melanoma has not been substantiated by further studies; marginal effects of this variant on the incidence of other cancers also need substantiating. Additionally, two recent studies have shown that this variant gives a similar-to-wild type response for resistance to DNA damage and homology-dependent repair [59,60].
- The variant Glu233Gly of *RAD51L3* could be a low-penetrance allele in high-risk breast cancer families without BRCA1/2 mutations [61].

The involvement of *RAD51* family members in cancer has also been assessed by looking at tumours for other consistent genetic alterations (mutations, loss of heterozygosity) and for gene expression changes. These data can be summarized as follows:

- **RAD51:** Examination of 45 Japanese breast cancer patients showed that two with synchronous bilateral onset had a G-to-A transition in the second nucleotide of codon 150 (protein change Arg150Gln). The family history of these patients was unclear, and the *BRCA* gene status not recorded, but this mutation was not found in 200 sporadic breast cancer cases [62]. Several loss-of-heterozygosity studies in tumour cells have implicated the chromosomal region including *RAD51* (15q15) [63-65], but this region contains many genes and in at least one case it was shown by further studies that the coding sequence and methylation status of the *RAD51* gene was unaffected [66]. Increased and decreased levels of *RAD51* expression in tumours have also been found. For example, decreased *RAD51* expression was found in 30% of

179 breast cancer cases (mostly sporadic, but some *BRCA1*-associated cases; [67]). However, in another study histological grading of sporadic invasive ductal breast cancer was found to correlate significantly with over-expression of wild-type *RAD51*, while the inverse was true for *BRCA1* expression [68]. Increased *RAD51* expression was also found in 66% of cases of pancreatic adenocarcinoma [69]. Microarray profiling of tumours has also detected alterations in gene expression of *RAD51*; for example, up-regulation in pancreatic cancer cell lines [70]. Recently, use of bone marrow samples from genetically-identical twins has shown down-regulation of *RAD51* associated with multiple myeloma [71].

- **RAD51L1** (also known as RAD51B, hREC2): Uterine leiomyomas commonly have a balanced translocation between chromosomes 12 and 14, with the high mobility group protein HMGA2 (also known as HMGIC) implicated as the chromosome 12 partner. Localization of the translocation on chromosome 14 showed that the breakpoint was within *RAD51L1* resulting in 3' truncation [72,73]. The key pathological product involved in these leiomyomas is still not clear; chimaeric transcripts encoding RAD51L1/HMGA2 fusion proteins have been detected in some studies [72,74], but rarely in others [75]. In uterine leiomyoma presenting with ascites and pleural fluid (pseudo-Meigs' syndrome) further studies support a 2-step model of tumorigenesis: the *HMGA2/RAD51L1* translocation in combination with a loss of the second *RAD51L1* allele [76]. *RAD51L1* has also been shown to be involved in the frequently-occurring translocation (6;14) in pulmonary chondroid hamartomas [77].
- **RAD51L2** (also known as RAD51C): The chromosomal region containing *RAD51L2* (17q23) has commonly been found to be amplified in sporadic breast cancers. Further analysis suggested that this amplification was associated with overexpression of *RAD51L2*, as well as several other linked genes, in a significant proportion of primary tumours [78,79].
- **XRCC2**: A dominant *XRCC2* mutation truncating the gene at codon 132 was found in a mismatch repair (MMR)-deficient cell line derived from a uterine sarcoma, but did not occur generally in MMR-deficient cell lines [80]. Screening a further 8 samples of uterine sarcomas revealed that one (a high grade leiomyosarcoma) had the same *XRCC2* mutation. This *XRCC2* mutation conferred HR deficiency and sensitivity to DNA-damaging agents. It was suggested that the mutator phenotype generated by MMR deficiency will lead to mutations in 'susceptible' genes such as *XRCC2*, which have mononucleotide sequence runs of >6 bases, generating further genetic instability which may be important in tumour progression [81]. In other direct sequencing studies, further rare heterozygous variants of *XRCC2* were not found to be associated with breast cancer [82].
- **XRCC3**: A heterozygous mutation in codon 213 (Asp213Asn) was found in DNA from 3/1577 healthy individuals. This mutation alters the highly conserved ATP-binding domain and completely abrogates gene function as shown by resistance to DNA damaging agents. However, Asp213Asn was not detected among 187 breast cancer families and 1300 unrelated patients with common cancers, providing no evidence for an influence on cancer risk [60].

These further data show some interesting potential associations of *RAD51*-like gene defects with cancer, especially with gynaecological tumours. It may be noted that there are also reports of an association of specific *BRCA1/2* mutations with uterine

cancers [83,84]. However, as with the study of natural *RAD51* family variants, most reports need independent verification with larger numbers of patients as well as laboratory studies to assess function.

6. Conclusions

There is still much to understand about the functions of the *RAD51* gene family and the consequences of their mutation or loss. While advances in the characterization of their protein activities are likely to be rapid, other relevant studies will take longer to realize. For example, as yet none of the variant genes has been tested in animal models, especially following treatment with DNA-damaging agents or in association with other gene defects. Having said this, the variant genes that have been analysed in humans do not appear to have dramatic effects on cancer incidence. Does this indicate that the RAD51 family genes, and perhaps the phenotype of genetic instability, are not important for cancer (see Introduction)? The reported studies may not be a good test of these questions, since mostly very subtle variants have been tested, and laboratory experiments show that these do not always give a detectable change in gene function. At the other extreme, where high levels of genetic instability occur, knocking out *RAD51* family genes is lethal for mice. Therefore it may be that mutations with an intermediate level of activity (including dominant negatives, as indicated in some of the above data) are the most influential in late-onset human conditions including cancer. Similarly, *BRCA1* or *BRCA2* knockout mice show embryonic lethality, while mice carrying certain hypomorphic mutations in these genes are susceptible to mammary cancer (review: [85]). Further understanding of the structure/function relationships of the RAD51 gene family will facilitate prediction of their role in destabilizing cells, while the use of animal models and more refined studies of cancer patients should properly define their influence on carcinogenesis.

Acknowledgements

The author is supported by the UK Medical Research Council and the European Commission (RISC-RAD contract F16R-CT-2003-508842).

References

[1] J.H. Hoeijmakers, Genome maintenance mechanisms for preventing cancer, Nature 411 (2001) 366-374.
[2] C.J. Sherr, Principles of tumor suppression, Cell 116 (2004) 235-246.
[3] L.A. Loeb, K.R. Loeb and J.P. Anderson, Multiple mutations and cancer, Proc Natl Acad Sci U S A 100 (2003) 776-781.
[4] O.M. Sieber, K. Heinimann and I.P. Tomlinson, Genomic instability--the engine of tumorigenesis?, Nat Rev Cancer 3 (2003) 701-708.
[5] P. Duesberg, A. Fabarius and R. Hehlmann, Aneuploidy, the primary cause of the multilateral genomic instability of neoplastic and preneoplastic cells, IUBMB Life 56 (2004) 65-81.
[6] D.L. Stoler, N. Chen, M. Basik, M.S. Kahlenberg, M.A. Rodriguez-Bigas, N.J. Petrelli and G.R. Anderson, The onset and extent of genomic instability in sporadic colorectal tumor progression, Proc Natl Acad Sci U S A 96 (1999) 15121-15126.
[7] B. Vogelstein and K.W. Kinzler, The multistep nature of cancer, Trends Genet 9 (1993) 138-141.
[8] S.C. West, Molecular views of recombination proteins and their control, Nat Rev Mol Cell Biol 4 (2003) 435-445.

[9] J. Thacker, A surfeit of RAD51-like genes?, Trends Genet 15 (1999) 166-168.
[10] J. Thacker, The role of homologous recombination processes in the repair of severe forms of DNA damage in mammalian cells, Biochimie 81 (1999) 77-85.
[11] L.H. Thompson and D. Schild, The contribution of homologous recombination in preserving genome integrity in mammalian cells, Biochimie 81 (1999) 87-105.
[12] C. Webber and C.P. Ponting, Genes and homology, Curr Biol 14 (2004) R332-333.
[13] M. Jasin, Homologous repair of DNA damage and tumorigenesis: the BRCA connection, Oncogene 21 (2002) 8981-8993.
[14] L. Pellegrini, D.S. Yu, T. Lo, S. Anand, M. Lee, T.L. Blundell and A.R. Venkitaraman, Insights into DNA recombination from the structure of a RAD51-BRCA2 complex, Nature 420 (2002) 287-293.
[15] T. Lo, L. Pellegrini, A.R. Venkitaraman and T.L. Blundell, Sequence fingerprints in BRCA2 and RAD51: implications for DNA repair and cancer, DNA Repair (Amst) 2 (2003) 1015-1028.
[16] D. Schild, Y. Lio, D.W. Collins, T. Tsomondo and D.J. Chen, Evidence for simultaneous protein interactions between human Rad51 paralogs, J Biol Chem 275 (2000) 16443-16449.
[17] J.P. Braybrooke, K.G. Spink, J. Thacker and I.D. Hickson, The RAD51 family member, RAD51L3, is a DNA-stimulated ATPase that forms a complex with XRCC2, J Biol Chem 275 (2000) 29100-29106.
[18] S. Sigurdsson, S. Van Komen, W. Bussen, D. Schild, J.S. Albala and P. Sung, Mediator function of the human Rad51B-Rad51C complex in Rad51/RPA-catalyzed DNA strand exchange, Genes Dev 15 (2001) 3308-3318.
[19] K.A. Miller, D.M. Yoshikawa, I.R. McConnell, R. Clark, D. Schild and J.S. Albala, RAD51C Interacts with RAD51B and Is Central to a Larger Protein Complex in Vivo Exclusive of RAD51, J Biol Chem 277 (2002) 8406-8411.
[20] J.Y. Masson, A.Z. Stasiak, A. Stasiak, F.E. Benson and S.C. West, Complex formation by the human RAD51C and XRCC3 recombination repair proteins, Proc Natl Acad Sci U S A 98 (2001) 8440-8446.
[21] H. Kurumizaka, S. Ikawa, M. Nakada, K. Eda, W. Kagawa, M. Takata, S. Takeda, S. Yokoyama and T. Shibata, Homologous-pairing activity of the human DNA-repair proteins Xrcc3.Rad51C, Proc Natl Acad Sci U S A 98 (2001) 5538-5543.
[22] C. Wiese, D.W. Collins, J.S. Albala, L.H. Thompson, A. Kronenberg and D. Schild, Interactions involving the Rad51 paralogs Rad51C and XRCC3 in human cells, Nucleic Acids Res 30 (2002) 1001-1008.
[23] J.Y. Masson, M.C. Tarsounas, A.Z. Stasiak, A. Stasiak, R. Shah, M.J. McIlwraith, F.E. Benson and S.C. West, Identification and purification of two distinct complexes containing the five RAD51 paralogs, Genes Dev 15 (2001) 3296-3307.
[24] N. Liu, D. Schild, M.P. Thelen and L.H. Thompson, Involvement of Rad51C in two distinct protein complexes of Rad51 paralogs in human cells, Nucleic Acids Res 30 (2002) 1009-1015.
[25] Y.C. Lio, A.V. Mazin, S.C. Kowalczykowski and D.J. Chen, Complex formation by the human Rad51B and Rad51C DNA repair proteins and their activities in vitro, J Biol Chem 278 (2003) 2469-2478.

[26] P. O'Regan, C. Wilson, S. Townsend and J. Thacker, XRCC2 is a nuclear RAD51-like protein required for damage-dependent RAD51 focus formation without the need for ATP binding, J Biol Chem 276 (2001) 22148-22153.
[27] C.A. French, C.E. Tambini and J. Thacker, Identification of functional domains in the RAD51L2 (RAD51C) protein and its requirement for gene conversion, J Biol Chem 278 (2003) 45445-45450.
[28] D.K. Bishop, U. Ear, A. Bhattacharyya, C. Calderone, M. Beckett, R.R. Weichselbaum and A. Shinohara, Xrcc3 is required for assembly of Rad51 complexes in vivo, J Biol Chem 273 (1998) 21482-21488.
[29] C.A. French, J.Y. Masson, C.S. Griffin, P. O'Regan, S.C. West and J. Thacker, Role of mammalian RAD51L2 (RAD51C) in recombination and genetic stability, J Biol Chem 277 (2002) 19322-19330.
[30] B.C. Godthelp, W.W. Wiegant, A. van Duijn-Goedhart, O.D. Scharer, P.P. van Buul, R. Kanaar and M.Z. Zdzienicka, Mammalian Rad51C contributes to DNA cross-link resistance, sister chromatid cohesion and genomic stability, Nucleic Acids Res 30 (2002) 2172-2182.
[31] H. Kurumizaka, S. Ikawa, M. Nakada, R. Enomoto, W. Kagawa, T. Kinebuchi, M. Yamazoe, S. Yokoyama and T. Shibata, Homologous pairing and ring and filament structure formation activities of the human Xrcc2*Rad51D complex, J Biol Chem 277 (2002) 14315-14320.
[32] Y. Liu, J.Y. Masson, R. Shah, P. O'Regan and S.C. West, RAD51C is required for Holliday junction processing in mammalian cells, Science 303 (2004) 243-246.
[33] M.A. Brenneman, B.M. Wagener, C.A. Miller, C. Allen and J.A. Nickoloff, XRCC3 controls the fidelity of homologous recombination: roles for XRCC3 in late stages of recombination, Mol Cell 10 (2002) 387-395.
[34] D.S. Lim and P. Hasty, A mutation in mouse rad51 results in an early embryonic lethal that is suppressed by a mutation in p53, Mol Cell Biol 16 (1996) 7133-7143.
[35] T. Tsuzuki, Y. Fujii, K. Sakumi, Y. Tominaga, K. Nakao, M. Sekiguchi, A. Matsushiro, Y. Yoshimura and MoritaT, Targeted disruption of the Rad51 gene leads to lethality in embryonic mice, Proc Natl Acad Sci U S A 93 (1996) 6236-6240.
[36] B. Deans, C.S. Griffin, M. Maconochie and J. Thacker, Xrcc2 is required for genetic stability, embryonic neurogenesis and viability in mice, Embo J 19 (2000) 6675-6685.
[37] Z. Shu, S. Smith, L. Wang, M.C. Rice and E.B. Kmiec, Disruption of muREC2/RAD51L1 in mice results in early embryonic lethality which can Be partially rescued in a p53(-/-) background, Mol Cell Biol 19 (1999) 8686-8693.
[38] D.L. Pittman and J.C. Schimenti, Midgestation lethality in mice deficient for the RecA-related gene, Rad51d/Rad51l3, Genesis 26 (2000) 167-173.
[39] E. Sonoda, M.S. Sasaki, J.M. Buerstedde, O. Bezzubova, A. Shinohara, H. Ogawa, M. Takata, Y. Yamaguchi-Iwai and S. Takeda, Rad51-deficient vertebrate cells accumulate chromosomal breaks prior to cell death, Embo J 17 (1998) 598-608.
[40] S.J. Xia, M.A. Shammas and R.J. Shmookler Reis, Elevated recombination in immortal human cells is mediated by HsRAD51 recombinase, Mol Cell Biol 17 (1997) 7151-7158.

[41] S. Vispe, C. Cazaux, C. Lesca and M. Defais, Overexpression of Rad51 protein stimulates homologous recombination and increases resistance of mammalian cells to ionizing radiation, Nucleic Acids Res 26 (1998) 2859-2864.
[42] C. Arnaudeau, T. Helleday and D. Jenssen, The RAD51 protein supports homologous recombination by an exchange mechanism in mammalian cells, J Mol Biol 289 (1999) 1231-1238.
[43] S. Lambert and B.S. Lopez, Characterization of mammalian RAD51 double strand break repair using non-lethal dominant-negative forms, Embo J 19 (2000) 3090-3099.
[44] P.M. Kim, C. Allen, B.M. Wagener, Z. Shen and J.A. Nickoloff, Overexpression of human RAD51 and RAD52 reduces double-strand break-induced homologous recombination in mammalian cells, Nucleic Acids Res 29 (2001) 4352-4360.
[45] C. Richardson, J.M. Stark, M. Ommundsen and M. Jasin, Rad51 overexpression promotes alternative double-strand break repair pathways and genome instability, Oncogene 23 (2004) 546-553.
[46] P. Bertrand, S. Lambert, C. Joubert and B.S. Lopez, Overexpression of mammalian Rad51 does not stimulate tumorigenesis while a dominant-negative Rad51 affects centrosome fragmentation, ploidy and stimulates tumorigenesis, in p53-defective CHO cells, Oncogene 22 (2003) 7587-7592.
[47] B. Deans, C.S. Griffin, P. O'Regan, M. Jasin and J. Thacker, Homologous recombination deficiency leads to profound genetic instability in cells derived from Xrcc2-knockout mice, Cancer Res 63 (2003) 8181-8187.
[48] C.S. Griffin, P.J. Simpson, C.R. Wilson and J. Thacker, Mammalian recombination-repair genes XRCC2 and XRCC3 promote correct chromosome segregation., Nature Cell Biol 2 (2000) 757-761.
[49] H.M. Hut, W. Lemstra, E.H. Blaauw, G.W. Van Cappellen, H.H. Kampinga and O.C. Sibon, Centrosomes split in the presence of impaired DNA integrity during mitosis, Mol Biol Cell 14 (2003) 1993-2004.
[50] M. Tarsounas, P. Munoz, A. Claas, P.G. Smiraldo, D.L. Pittman, M.A. Blasco and S.C. West, Telomere maintenance requires the RAD51D recombination/repair protein, Cell 117 (2004) 337-347.
[51] A.R. Venkitaraman, Chromosome stability, DNA recombination and the BRCA2 tumour suppressor, Curr Opin Cell Biol 13 (2001) 338-343.
[52] M. Kraakman-van der Zwet, W.J. Overkamp, R.E. van Lange, J. Essers, A. van Duijn-Goedhart, I. Wiggers, S. Swaminathan, P.P. van Buul, A. Errami, R.T. Tan, N.G. Jaspers, S.K. Sharan, R. Kanaar and M.Z. Zdzienicka, Brca2 (XRCC11) deficiency results in radioresistant DNA synthesis and a higher frequency of spontaneous deletions, Mol Cell Biol 22 (2002) 669-679.
[53] A. Tutt, A. Gabriel, D. Bertwistle, F. Connor, H. Paterson, J. Peacock, G. Ross and A. Ashworth, Absence of Brca2 causes genome instability by chromosome breakage and loss associated with centrosome amplification, Curr Biol 9 (1999) 1107-1110.
[54] X. Xu, Z. Weaver, S.P. Linke, C. Li, J. Gotay, X.W. Wang, C.C. Harris, T. Ried and C.X. Deng, Centrosome amplification and a defective G2-M cell cycle checkpoint induce genetic instability in BRCA1 exon 11 isoform-deficient cells, Mol Cell 3 (1999) 389-395.
[55] M.J. Difilippantonio, J. Zhu, H.T. Chen, E. Meffre, M.C. Nussenzweig, E.E. Max, T. Ried and A. Nussenzweig, DNA repair protein Ku80 suppresses

chromosomal aberrations and malignant transformation, Nature 404 (2000) 510-514.
[56] H.W. Mohrenweiser, D.M. Wilson, 3rd and I.M. Jones, Challenges and complexities in estimating both the functional impact and the disease risk associated with the extensive genetic variation in human DNA repair genes, Mutat Res 526 (2003) 93-125.
[57] T. Xi, I.M. Jones and H.W. Mohrenweiser, Many amino acid substitution variants identified in DNA repair genes during human population screenings are predicted to impact protein function, Genomics 83 (2004) 970-979.
[58] S. Rafii, P. O'Regan, G. Xinarianos, I. Azmy, T. Stephenson, M. Reed, M. Meuth, J. Thacker and A. Cox, A potential role for the XRCC2 R188H polymorphic site in DNA-damage repair and breast cancer, Hum Mol Genet 11 (2002) 1433-1438.
[59] F.D. Araujo, A.J. Pierce, J.M. Stark and M. Jasin, Variant XRCC3 implicated in cancer is functional in homology-directed repair of double-strand breaks, Oncogene 21 (2002) 4176-4180.
[60] S. Rafii, A. Lindblom, M. Reed, M. Meuth and A. Cox, A naturally occurring mutation in an ATP-binding domain of the recombination repair gene XRCC3 ablates its function without causing cancer susceptibility, Hum Mol Genet 12 (2003) 915-923.
[61] R. Rodriguez-Lopez, A. Osorio, G. Ribas, M. Pollan, L. Sanchez-Pulido, M. de la Hoya, A. Ruibal, P. Zamora, J.I. Arias, R. Salazar, A. Vega, J.I. Martinez, E. Esteban-Cardenosa, C. Alonso, R. Leton, M. Urioste Azcorra, C. Miner, M.E. Armengod, A. Carracedo, R. Gonzalez-Sarmiento, T. Caldes, O. Diez and J. Benitez, The variant E233G of the RAD51D gene could be a low-penetrance allele in high-risk breast cancer families without BRCA1/2 mutations, Int J Cancer 110 (2004) 845-849.
[62] M. Kato, K. Yano, F. Matsuo, H. Saito, T. Katagiri, H. Kurumizaka, M. Yoshimoto, F. Kasumi, F. Akiyama, G. Sakamoto, H. Nagawa, Y. Nakamura and Y. Miki, Identification of Rad51 alteration in patients with bilateral breast cancer, J Hum Genet 45 (2000) 133-137.
[63] W. Wick, I. Petersen, R.K. Schmutzler, B. Wolfarth, D. Lenartz, E. Bierhoff, J. Hummerich, D.J. Muller, A.P. Stangl, J. Schramm, O.D. Wiestler and A. von Deimling, Evidence for a novel tumor suppressor gene on chromosome 15 associated with progression to a metastatic stage in breast cancer, Oncogene 12 (1996) 973-978.
[64] R. Gonzalez, J.M. Silva, G. Dominguez, J.M. Garcia, G. Martinez, J. Vargas, M. Provencio, P. Espana and F. Bonilla, Detection of loss of heterozygosity at RAD51, RAD52, RAD54 and BRCA1 and BRCA2 loci in breast cancer: pathological correlations, Br J Cancer 81 (1999) 503-509.
[65] C.Y. Shen, J.C. Yu, Y.L. Lo, C.H. Kuo, C.T. Yue, Y.S. Jou, C.S. Huang, J.C. Lung and C.W. Wu, Genome-wide search for loss of heterozygosity using laser capture microdissected tissue of breast carcinoma: an implication for mutator phenotype and breast cancer pathogenesis, Cancer Res 60 (2000) 3884-3892.
[66] C. Schmutte, G. Tombline, K. Rhiem, M.M. Sadoff, R. Schmutzler, A. von Deimling and R. Fishel, Characterization of the human Rad51 genomic locus and examination of tumors with 15q14-15 loss of heterozygosity (LOH), Cancer Res 59 (1999) 4564-4569.

[67] K. Yoshikawa, T. Ogawa, R. Baer, H. Hemmi, K. Honda, A. Yamauchi, T. Inamoto, K. Ko, S. Yazumi, H. Motoda, H. Kodama, S. Noguchi, A.F. Gazdar, Y. Yamaoka and R. Takahashi, Abnormal expression of BRCA1 and BRCA1-interactive DNA-repair proteins in breast carcinomas, Int J Cancer 88 (2000) 28-36.
[68] H. Maacke, S. Opitz, K. Jost, W. Hamdorf, W. Henning, S. Kruger, A.C. Feller, A. Lopens, K. Diedrich, E. Schwinger and H.W. Sturzbecher, Over-expression of wild-type Rad51 correlates with histological grading of invasive ductal breast cancer, Int J Cancer 88 (2000) 907-913.
[69] H. Maacke, K. Jost, S. Opitz, S. Miska, Y. Yuan, L. Hasselbach, J. Luttges, H. Kalthoff and H.W. Sturzbecher, DNA repair and recombination factor Rad51 is over-expressed in human pancreatic adenocarcinoma, Oncogene 19 (2000) 2791-2795.
[70] H. Han, D.J. Bearss, L.W. Browne, R. Calaluce, R.B. Nagle and D.D. Von Hoff, Identification of differentially expressed genes in pancreatic cancer cells using cDNA microarray, Cancer Res 62 (2002) 2890-2896.
[71] N.C. Munshi, T. Hideshima, D. Carrasco, M. Shammas, D. Auclair, F. Davies, N. Mitsiades, C. Mitsiades, R.S. Kim, C. Li, S.V. Rajkumar, R. Fonseca, L. Bergsagel, D. Chauhan and K.C. Anderson, Identification of genes modulated in multiple myeloma using genetically identical twin samples, Blood 103 (2004) 1799-1806.
[72] E.F. Schoenmakers, C. Huysmans and W.J. Van de Ven, Allelic knockout of novel splice variants of human recombination repair gene RAD51B in t(12;14) uterine leiomyomas, Cancer Res 59 (1999) 19-23.
[73] S.E. Ingraham, R.A. Lynch, S. Kathiresan, A.J. Buckler and A.G. Menon, hREC2, a RAD51-like gene, is disrupted by t(12;14) (q15;q24.1) in a uterine leiomyoma, Cancer Genet Cytogenet 115 (1999) 56-61.
[74] T. Takahashi, N. Nagai, H. Oda, K. Ohama, N. Kamada and K. Miyagawa, Evidence for RAD51L1/HMGIC fusion in the pathogenesis of uterine leiomyoma, Genes Chromosomes Cancer 30 (2001) 196-201.
[75] B.J. Quade, S. Weremowicz, D.M. Neskey, R. Vanni, C. Ladd, P. Dal Cin and C.C. Morton, Fusion transcripts involving HMGA2 are not a common molecular mechanism in uterine leiomyomata with rearrangements in 12q15, Cancer Res 63 (2003) 1351-1358.
[76] F. Amant, M. Debiec-Rychter, E.F. Schoenmakers, A. Hagemeijer-Hausman and I. Vergote, Cumulative dosage effect of a RAD51L1/HMGA2 fusion and RAD51L1 loss in a case of pseudo-Meigs' syndrome, Genes Chromosomes Cancer 32 (2001) 324-329.
[77] C. Blank, E.F. Schoenmakers, P. Rogalla, E.H. Huys, A.A. van Rijk, N. Drieschner and J. Bullerdiek, Intragenic breakpoint within RAD51L1 in a t(6;14)(p21.3;q24) of a pulmonary chondroid hamartoma, Cytogenet Cell Genet 95 (2001) 17-19.
[78] G.J. Wu, C.S. Sinclair, J. Paape, J.N. Ingle, P.C. Roche, C.D. James and F.J. Couch, 17q23 amplifications in breast cancer involve the PAT1, RAD51C, PS6K, and SIGma1B genes, Cancer Res 60 (2000) 5371-5375.
[79] M. Barlund, O. Monni, J. Kononen, R. Cornelison, J. Torhorst, G. Sauter, O.-P. Kallioniemi and A. Kallioniemi, Multiple genes at 17q23 undergo amplification and overexpression in breast cancer, Cancer Res 60 (2000) 5340-5344.

[80] A. Mohindra, L.E. Hays, E.N. Phillips, B.D. Preston, T. Helleday and M. Meuth, Defects in homologous recombination repair in mismatch-repair-deficient tumour cell lines, Hum Mol Genet 11 (2002) 2189-2200.
[81] A. Mohindra, E. Bolderson, J. Stone, M. Wells, T. Helleday and M. Meuth, A tumour-derived mutant allele of XRCC2 preferentially suppresses homologous recombination at DNA replication forks, Hum Mol Genet 13 (2004) 203-212.
[82] R. Rodriguez-Lopez, A. Osorio, L. Sanchez-Pulido, M. De La Hoya, A. Barroso, T. Caldes and J. Benitez, No mutations in the XRCC2 gene in BRCA1/2-negative high-risk breast cancer families, Int J Cancer 103 (2003) 136-137.
[83] S.N. Agoff, J.E. Mendelin, V.S. Grieco and R.L. Garcia, Unexpected gynecologic neoplasms in patients with proven or suspected BRCA-1 or -2 mutations: implications for gross examination, cytology, and clinical follow-up, Am J Surg Pathol 26 (2002) 171-178.
[84] O. Lavie, G. Hornreich, A. Ben-Arie, G. Rennert, Y. Cohen, R. Keidar, S. Sagi, E.L. Lahad, R. Auslander and U. Beller, BRCA germline mutations in Jewish women with uterine serous papillary carcinoma, Gynecol Oncol 92 (2004) 521-524.
[85] M.E. Moynahan, The cancer connection: BRCA1 and BRCA2 tumor suppression in mice and humans, Oncogene 21 (2002) 8994-9007.
[86] W.W. Wang, A.B. Spurdle, P. Kolachana, B. Bove, B. Modan, S.M. Ebbers, G. Suthers, M.A. Tucker, D.J. Kaufman, M.M. Doody, R.E. Tarone, M. Daly, H. Levavi, H. Pierce, A. Chetrit, G.H. Yechezkel, G. Chenevix-Trench, K. Offit, A.K. Godwin and J.P. Struewing, A single nucleotide polymorphism in the 5' untranslated region of RAD51 and risk of cancer among BRCA1/2 mutation carriers, Cancer Epidemiol Biomarkers Prev 10 (2001) 955-960.
[87] E. Levy-Lahad, A. Lahad, S. Eisenberg, E. Dagan, T. Paperna, L. Kasinetz, R. Catane, B. Kaufman, U. Beller, P. Renbaum and R. Gershoni-Baruch, A single nucleotide polymorphism in the RAD51 gene modifies cancer risk in BRCA2 but not BRCA1 carriers, Proc Natl Acad Sci U S A 98 (2001) 3232-3236.
[88] L. Kadouri, Z. Kote-Jarai, A. Hubert, F. Durocher, D. Abeliovich, B. Glaser, T. Hamburger, R.A. Eeles and T. Peretz, A single-nucleotide polymorphism in the RAD51 gene modifies breast cancer risk in BRCA2 carriers, but not in BRCA1 carriers or noncarriers, Br J Cancer 90 (2004) 2002-2005.
[89] A. Jakubowska, S.A. Narod, D.E. Goldgar, M. Mierzejewski, B. Masojc, K. Nej, J. Huzarska, T. Byrski, B. Gorski and J. Lubinski, Breast cancer risk reduction associated with the RAD51 polymorphism among carriers of the BRCA1 5382insC mutation in Poland, Cancer Epidemiol Biomarkers Prev 12 (2003) 457-459.
[90] B. Kuschel, A. Auranen, S. McBride, K.L. Novik, A. Antoniou, J.M. Lipscombe, N.E. Day, D.F. Easton, B.A. Ponder, P.D. Pharoah and A. Dunning, Variants in DNA double-strand break repair genes and breast cancer susceptibility, Hum Mol Genet 11 (2002) 1399-1407.
[91] J. Han, S.E. Hankinson, S.M. Zhang, I. De Vivo and D.J. Hunter, Interaction between genetic variations in DNA repair genes and plasma folate on breast cancer risk, Cancer Epidemiol Biomarkers Prev 13 (2004) 520-524.
[92] J. Han, S.E. Hankinson, H. Ranu, I. De Vivo and D.J. Hunter, Polymorphisms in DNA double-strand break repair genes and breast cancer risk in the Nurses' Health Study, Carcinogenesis 25 (2004) 189-195.

[93] J. Han, G.A. Colditz, L.D. Samson and D.J. Hunter, Polymorphisms in DNA double-strand break repair genes and skin cancer risk, Cancer Res 64 (2004) 3009-3013.
[94] S.L. Winsey, N.A. Haldar, H.P. Marsh, M. Bunce, S.E. Marshall, A.L. Harris, F. Wojnarowska and K.I. Welsh, A variant within the DNA repair gene XRCC3 is associated with the development of melanoma skin cancer, Cancer Res 60 (2000) 5612-5616.
[95] G. Matullo, S. Guarrera, S. Carturan, M. Peluso, C. Malaveille, L. Davico, A. Piazza and P. Vineis, DNA repair gene polymorphisms, bulky DNA adducts in white blood cells and bladder cancer in a case-control study, Int J Cancer 92 (2001) 562-567.
[96] G.L. David-Beabes, R.M. Lunn and S.J. London, No association between the XPD (Lys751G1n) polymorphism or the XRCC3 (Thr241Met) polymorphism and lung cancer risk, Cancer Epidemiol Biomarkers Prev 10 (2001) 911-912.
[97] Z. Duan, H. Shen, J.E. Lee, J.E. Gershenwald, M.I. Ross, P.F. Mansfield, M. Duvic, S.S. Strom, M.R. Spitz and Q. Wei, DNA repair gene XRCC3 241Met variant is not associated with risk of cutaneous malignant melanoma, Cancer Epidemiol Biomarkers Prev 11 (2002) 1142-1143.
[98] M.C. Stern, D.M. Umbach, R.M. Lunn and J.A. Taylor, DNA repair gene XRCC3 codon 241 polymorphism, its interaction with smoking and XRCC1 polymorphisms, and bladder cancer risk, Cancer Epidemiol Biomarkers Prev 11 (2002) 939-943.
[99] H. Shen, E.M. Sturgis, K.R. Dahlstrom, Y. Zheng, M.R. Spitz and Q. Wei, A variant of the DNA repair gene XRCC3 and risk of squamous cell carcinoma of the head and neck: a case-control analysis, Int J Cancer 99 (2002) 869-872.
[100] T.R. Smith, M.S. Miller, K. Lohman, E.M. Lange, L.D. Case, H.W. Mohrenweiser and J.J. Hu, Polymorphisms of XRCC1 and XRCC3 genes and susceptibility to breast cancer, Cancer Lett 190 (2003) 183-190.
[101] Y. Wang, D. Liang, M.R. Spitz, K. Zhang, Q. Dong, C.I. Amos and X. Wu, XRCC3 genetic polymorphism, smoking, and lung carcinoma risk in minority populations, Cancer 98 (2003) 1701-1706.
[102] N.R. Jacobsen, B.A. Nexo, A. Olsen, K. Overvad, H. Wallin, A. Tjonneland and U. Vogel, No association between the DNA repair gene XRCC3 T241M polymorphism and risk of skin cancer and breast cancer, Cancer Epidemiol Biomarkers Prev 12 (2003) 584-585.
[103] C.G. Bertram, R.M. Gaut, J.H. Barrett, J. Randerson-Moor, L. Whitaker, F. Turner, V. Bataille, I. dos Santos Silva, A.J. Swerdlow, D.T. Bishop and J.A. Newton Bishop, An assessment of a variant of the DNA repair gene XRCC3 as a possible nevus or melanoma susceptibility genotype, J Invest Dermatol 122 (2004) 429-432.
[104] J.C. Figueiredo, J.A. Knight, L. Briollais, I.L. Andrulis and H. Ozcelik, Polymorphisms XRCC1-R399Q and XRCC3-T241M and the risk of breast cancer at the Ontario site of the Breast Cancer Family Registry, Cancer Epidemiol Biomarkers Prev 13 (2004) 583-591.