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Review Article

DNA Signalling/Repair Genetic Polymorphisms and Breast Cancer Risk: a Review

Sandra Costa,[1] Rui Medeiros,[2,3] Fernando Schmitt[1,4]

[1] ICVS, Life and Health Sciences Research Institute, Health Science School, Minho University, Braga, Portugal

[2] Molecular Oncology Unit, Portuguese Institute of Oncology - Porto, Porto, Portugal

[3] ICBAS, Abel Salazar Institute for the Biomedical Sciences, Porto, Portugal

[4] Medical Faculty of Porto University and IPATIMUP, Institute of Molecular Pathology and Immunology of the University of Porto, Porto, Portugal

Abstract

Breast cancer is the leading cause of death among women in developing countries. In Portugal, it presents the highest incidence and mortality rates in women diseases. About 10% of breast cancer is inherited, presenting a family pattern of incidence, and have been attributable to mutations in high penetrance susceptibility genes, such as *BRCA1* and *BRCA2*. However, *BRCA1* and *BRCA2* mutations account only for around 25% of families with inherited breast cancer. Many environmental factors have been associated with risk of breast cancer development, such as ionized radiation, chemical carcinogens (diet and environment). These mutagens sources, together with endogenous and exogenous estrogens, produce a range of DNA lesions such as reactive oxygen species, oxidized bases, bulky DNA adducts and DNA strand breaks. Therefore, DNA repair capacity determines cellular susceptibility to endogenous and exogenous substances and factors. The response of cells to DNA damage and their ability to maintain genomic instability by DNA repair are crucial in preventing cancer initiation and progression. Some studies have demonstrated a strong association of higher levels of DNA damage and lower DNA repair capacity in breast cancer patients and healthy women with a positive family history of breast cancer. Several polymorphisms have been described in DNA signalling and repair genes. Therefore, although each polymorphism may be associated with a small increased risk for breast cancer in an individual, the risk attributable in the population as a whole is likely to be higher than for rare, high-penetrance susceptibility genes. In this review, we intend to illustrate the state of the art in studies concerning DNA signalling or repair genetic polymorphisms and breast cancer susceptibility.

Key words: Bone neoplasms. Osteosarcoma. Cartilaginous tumours. Osteochondroma. Chondrosarcoma.

Introduction

Breast cancer is the leading cause of death among women in developing countries. Portugal presents the highest incidence and mortality rates in women diseases.[1] According to the World Health Organization, more than 1.2 million people worldwide will be diagnosed with breast cancer this year. Well-established risk factors have been described to breast cancer, such as early menarche, late menopause, age of first child's birth, nulliparity and family history.[2] However, these factors account for a little percentage of breast cancer cases, being the majority of cases attributable to other risk factors. Approximately 10% of all breast cancer is

Correspondence
Fernando Schmitt
Rua Dr. Roberto Frias s/n
4200-465 Porto, Portugal
Phone: 351 22 55070700
Fax: 351 22 55070799
E-mail: fschmitt@ipatimup.pt

inherited, presenting a family pattern of incidence, and have been attributable to mutations in high penetrance susceptibility genes, such as *BRCA1* and *BRCA2*. However, *BRCA1* and *BRCA2* mutations account only for around 25% of families with inherited breast cancer.[3] The majority of breast cancer cases do not have any inherited origin neither germ line mutations. In this way, identification of genes that are associated with a small or moderate cancer risk is an important step in defining breast cancer risk. It has been understood that different genetic backgrounds due to the combination of subtle sequence variants or polymorphisms, the low-penetrance genes, could explain the remaining familial and "sporadic" breast cancer risks.

Many environmental factors have been associated with risk of breast cancer development, such as ionized radiation and chemical carcinogens (diet and environment).[4-6] These mutagens sources, together with endogenous and exogenous estrogens, produce a range of DNA lesions such as reactive oxygen species, oxidized bases, bulky DNA adducts and DNA strand breaks.[7,8] Mammalian cells have evolved distinct pathways to repair different types of DNA damage and maintain genome integrity. Therefore, DNA repair capacity determines cellular susceptibility to endogenous and exogenous substances and factors. The response of the cells to DNA damage and their ability to maintain genomic instability by DNA repair are crucial in preventing cancer initiation and progression. Some studies have demonstrated a strong association of higher levels of DNA damage and lower DNA repair capacity in breast cancer patients and healthy women with a positive family history of breast cancer.[9-11]

Several studies have shown the presence of polymorphic alleles in DNA repair genes, and they have been identified in exonic and/or promoter regions in at least 37 DNA repair genes, including genes of Base Excision Repair (BER), Nucleotide Excision Repair (NER) and Double Strand Break Repair (DSBR) pathways. Previous studies have suggested an influence of variants in genes of the different DNA repair pathways in the DNA repair capacity and/or fidelity. Therefore, polymorphisms in these genes may represent important factors to breast cancer susceptibility.

DNA Repair Pathways

The importance of DNA repair is underscored by DNA repair deficiency, which is associated with hypersensibility to DNA-damaging agents and accumulation of mutations in the genome,[12] and with genomic instability syndromes, which dramatically increase cancer incidence.[13] Approximately 150 human DNA repair genes were cloned and sequenced. DNA repair genes can be divided into 2 sub-groups: genes associated with signalling and regulation of DNA repair, and genes associated with distinct repair mechanisms, such as BER, NER, DSBR, mismatch repair (MMR) and direct damage reversal. In this review, we will just focus on the DNA repair pathways more related with breast cancer initiation and progression, namely BER, NER and DSBR and DNA damage signalling and regulation.

DNA damage signalling

Fidelity of the eukaryotic genome is maintained by coordinated actions of cellular pathways, including DNA repair, chromatin remodelling, apoptosis, and cell cycle checkpoints. The checkpoint pathways are signal-transduction pathways, responsible mainly for the control of cell cycle arrest, control of the activation of DNA repair pathways, movement of DNA repair proteins to sites of DNA damage, activation of transcriptional programmes and induction of cell death by apoptosis.[14] These DNA damage control mechanisms minimize the risk of DNA lesions being converted to inheritable mutations, and are believed to be of critical importance in carcinogenesis.

As in all signal-transduction pathways, DNA checkpoint pathways involve sensors, responsible for DNA damage recognition and signal initiation, transducers, being in charge of transmitting and amplifying the signal, and effector molecules, that control the biological consequences of triggering the pathway (Figure 1).

In mammalian systems, the proteins responsible for the sensing and initiation of DNA damage responses, caused by various genotoxic agents, are two protein kinases of the PI-3-kinase-like kinase family: ATM (*ataxia telangiectasia* mutated) and ATR (*ATM- and Rad3-related*). The

kinase activity of ATM is activated when DNA double-strand breaks occur.[15,16] A crucial sensor for the ATM pathway seems to be the MRE11-NBS1-RAD50 complex. This complex is required for [1]the damage-induced chromatin association of ATM and for efficient ATM autophosphorilation after damage.[16] In contrast to ATM, the ATR responds to types of damage rather than DSB, such that caused by hydroxyurea and UV-light.[14] Activation of the ATR kinase requires its associated protein ATRIP and two protein complexes, that seem to be the trimeric proliferating cell nuclear antigen (PCNA) and the replication factor C (RFC).[16]

Some proteins are crucial to the activation of specific subsets of ATM or ATR substrates, and because of this designated mediators. ATR-dependent pathway requires the function of several proteins including BRCA1, Claspin and MDC1. In the case of ATM, 53BP1 and MDC1 also appear to be critical for the phosphorilation of many ATM substrates.[16]

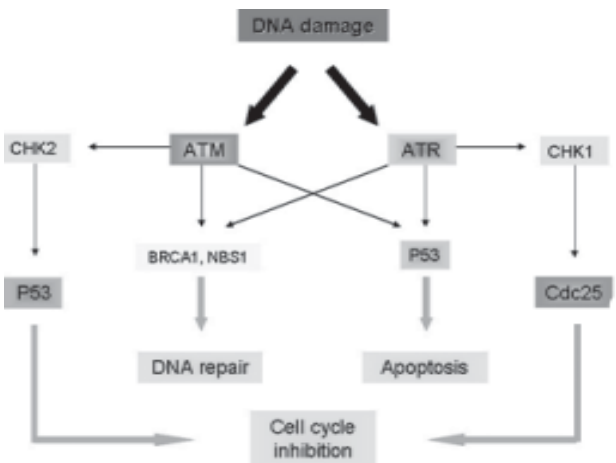

Figure 1 – Simplified scheme of DNA damage signalling

With the help of mediators, checkpoint signals are transmitted, in the form of protein phosphorilation, to two major signal-transducing kinases—CHK1 and CHK2. These two kinases regulate in turn downstream targets, such as Cdc25A, Cdc25C, and P53, to control cell cycle progression and DNA synthesis. CHK2 is the kinase target of ATM, and seems to phosphorilate P53 and BRCA1.[14,17] On the other side, CHK1 is the target of ATR-dependent pathway and responsible for Cdc25 phosphorilation.[16,17]

Base Excision Repair (BER)

BER is responsible for the repair of lesions such as oxidized DNA bases, arising spontaneously within the cell or from exposure to exogenous agents, including ionising radiation and long-wave UV light, and DNA alkylation induced by endogenous alkylating species and exogenous carcinogens.[18] Briefly, BER is initiated by a DNA glycosylase that releases the target base to form an abasic site (AP) in the DNA (Figure 2). AP endonuclease (APE1) is the second enzyme in the pathway and hydrolyses the phosphosdiester bond 5′ to the abasic site to generate a nick. The insertion of the first nucleotide is performed by DNA polymerase b (Polb).[19] The removal of 5′dRP upon the insertion of the first nucleotide is the critical step in the decision between the two sub-pathways in BER: short-patch or long-patch. Besides polymerisation activity, Polb also exerts lyase activity in the hemiacetal form of 5′-dRP residues from incised AP sites. In contrast, oxidised or reduced AP sites are resistant to b elimination by Polb. Upon dissociation of Polb from damaged DNA, strand displacement and DNA synthesis are accomplished by Pole and Pold together with PCNA and RF-C, resulting in longer repair patches of up to 10 nucleotides. The removal of deoxyribosephosphate flap structure is executed by flap endonuclease FEN1 stimulated by PCNA. The ligation is performed by ligase I, in interaction with PCNA and Polb, in long-patch BER, and by ligase III, that interact with XRCC1, Polb and PARP-1 [poly(ADP-ribose) polymerase-1], in short-patch BER.[18,19]

Nucleotide Excision Repair

NER is the major repair system for removing bulky DNA lesions, such as UV-light-induced photolesions and cyclobutane pyrimidine dimers, intrastrand cross-links and large chemical adducts generated from exposure to genotoxic agents.[20] This pathway consists of 2 distinct sub-pathways designated global genomic repair (GGR) and transcription-coupled repair (TCR). GGR seems to be responsible for the repair of the non-transcribed domains of the genome. In contrast, TCR removes lesions from the transcribed strand of active genes. The first step involved in NER is the recognition of damaged residues and bubble

formation, performed by XPC-hHR23B and the nine subunits of TFIIH, XPA and RPA, respectively (Figure 3). The dual incision of the damaged DNA strands 5′ and 3′ to the lesion is executed by 2 endonucleases, XPG and ERCC1-XPF. DNA polymerases Pold and Pole jointly with the sliding clamp PCNA, the pentameric clamp loader RFC and DNA ligase I, are responsible for the release of an oligonucleotide containing the damage, synthesis and ligation of the resulting gap. With the exception of XPC-hHR23B, all genes involved in GGR are also required for TCR. In addition, TCR requires other genes, including CSA and CSB genes.[18,19]

Three rare autosomal recessive disorders are associated with a defect in NER: xeroderma pigmentosum (XP), cockayne syndrome (CS) and trichothiodystrophy (TTD). While xeroderma pigmentosum patients have a partial or total defect in GGR and also TCR, cockayne syndrome and trichothiodystrophy patients present defects only in TCR. The three conditions display pleiotropic phenotypes and share an extreme sensitivity to sunlight, and in the same cases an increased predisposition to some types of cancers.[13]

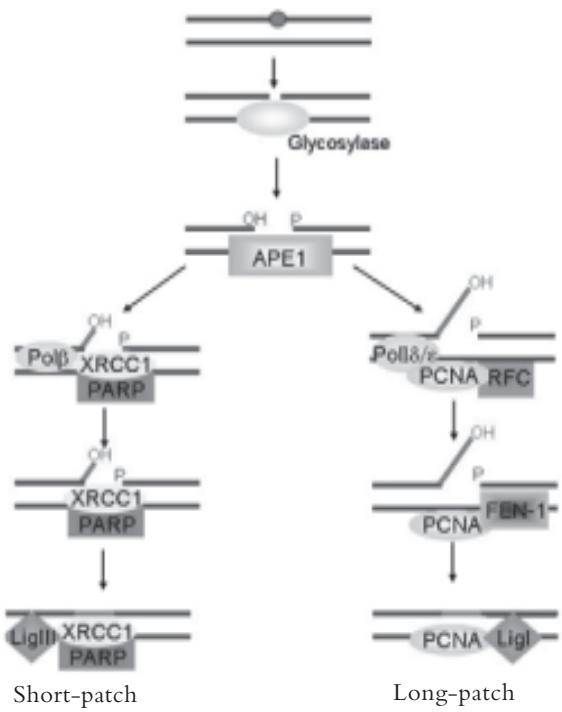

Figure 2 – Simplified scheme of short and long-patch BER pathway

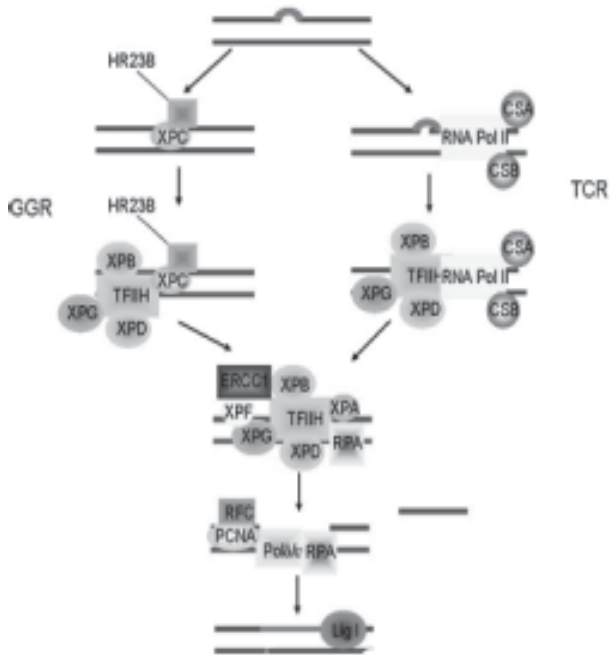

Figure 3 – Simplified scheme of NER pathways: GGR and TCR

Double-Strand Break Repair (DSBR)

DSB are produced by reactive oxygen species, ionizing radiation and chemicals that produced these substances. The repair of DSB involves 2 types of pathways (figure 4): homologous recombination (HR) and nonhomologous end-joining (NHEJ) mechanisms, which are error-free and error-prone, respectively. The occurrence of HR or NHEJ depends on the cell cycle phase. HR occurs during the late S and G2 phases, whereas NHEJ occurs mainly in G0/G1 phases.[18]

HR pathway uses extensive regions of DNA homology as coding information. The homologous DNA is usually the sister cromatid but may be the homologous chromosome. The first step in HR is the nucleolytic resection of the DSB in the 5′-3′ direction by the MRE11-Rad50-NBS1 complex. The resulting 3′ single-stranded DNA is bound by a heptameric ring complex formed by Rad52 proteins. The search for a homologous template and the formation of the joint molecules are performed by Rad51 nucleoprotein filament, whose reunion is facilitated by five different paralogues of Rad51 (Rad51B, C and D, XRCC2 and XRCC3). The BRCA2 interacts directly with

RAD51, through its BRC repeats and through a domain in its carboxyl terminus.[21,22] The interaction between these molecules is essential to RAD51 nucleoprotein filament formation.[23] Furthermore, the BRCA1, having important functions in DNA damage checkpoints, seems to be important to RAD51 functions, but the nature of this interaction is still unknown. After strand exchange, the resulting structures are resolved according to the classical model of Holliday.[24]

In contrast to HR, NHEJ is a conceptually simple pathway that involves the religation of broken ends and does not require a homologous template.[25] NHEJ is initiated by the binding of a heterodimer complex consisting of the Ku70 and Ku80 proteins to the damaged DNA, protecting DNA from exonucleases digestion. The Ku heterodimer associates with the catalytic subunit of DNA-PK. One of the targets of DNA-PKs is XRCC4, which forms a stable complex with DNA ligase IV, which binds to the ends of DNA molecules and links duplex DNA molecules with complementary but non-ligatable ends. The XRCC4-ligase IV complex cannot directly re-ligate most DSB, being these processed first. The processing of DSB is mainly performed by MRE11-Rad50-NBS1 complex. Two others proteins that seem to be involved in the removal of 5′ and 3′ overhang are FEN1 and Artemis.[25]

DNA repair capacity and breast cancer risk

Impaired DNA repair may fuel up malignant transformation of breast cells due to the accumulation of spontaneous mutations in target genes and increasing susceptibility to exogenous carcinogens. Moreover, the effectiveness of DNA repair may contribute to the failure of chemotherapy and resistance of breast cancer cells to drugs and radiation.

A variety of biomarkers have been used to analyse DNA repair capacities that are based on the measurement of biological activities as a consequence of DNA repair deficiencies.[26,27] The choice of the method to use depends mainly on the source and nature of the DNA damage. DNA damage detection techniques, such as cytogenetic measurements (chromosomal aberrations, micronuclei and sister chromatid exchanges), host cell reactivation assay (HCR), alkaline comet assay and antibody based assays, have been used to show the contribution of higher levels of DNA damage and DNA repair deficiencies to breast carcinogenesis.

A range of DNA lesions, namely reactive oxygen species, oxidized bases, bulky DNA adducts and DNA single and double-strand breaks[7,8] result from etiologic agents (such as

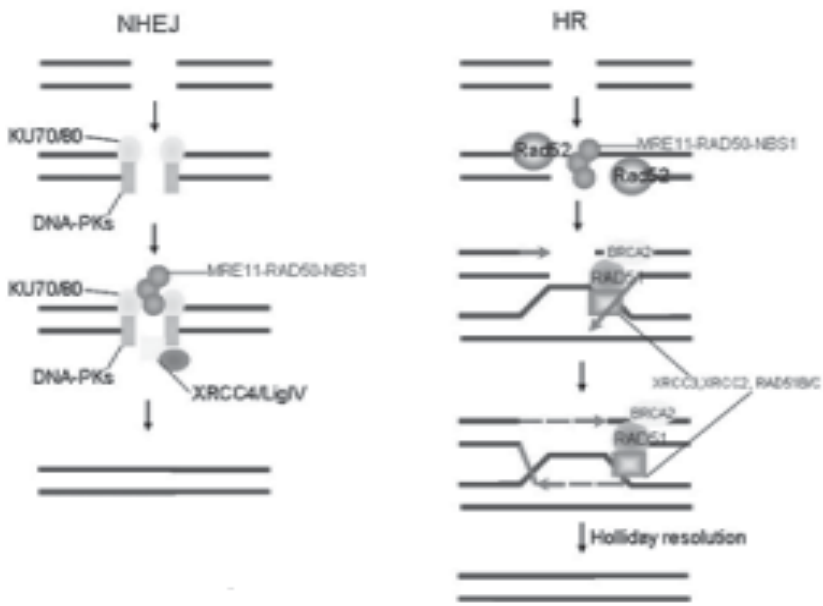

Figure 4 – Simplified scheme of DSR repair pathways: HR and NHEJ

Table 1 – DNA repair capacity in breast cancer patients compared with healthy women in different DNA damage induced assays (FH – family history; FDR - first degree relative)

Reference	Damaging Agent	Detection Assay	DNA damage Cases (n) FH	No FH	Controls (n) FH or FDR	No FH
Patel et al. 1997[28]	X-irradiation	Cytogenetic measurements		159.64 (14)*	135.89 (19)*	91.94 (17)
Jyothish et al. 1998[9]	Bleomycin	Cytogenetic measurements	1.2819 (36)*	0.8189 (36)*	0.7935 (85)*	0.570 (40)
Rajeswari et al. 2000[30]	MNNG	Alkaline comet assay		13.49 (88)*	5.98 (188)*	2.48 (121)
Buchholz et al. 2001[10]	g-irradiation	Cytogenetic measurements	0.67 (17)*	0.49 (8)		0.45(18)
Smith et al. 2003[27]	Basal damage g-radiation 10 min after radiation	Alkaline comet assay		10.78 (70)* 21.24 (70)* 14.76 (70)*		6.86 (70) 14.97 (70) 9.75 (70)
Kennedy et al. 2005[34]	BPDE	Immunohistochemical assay		26.5% (158)*		35.1% (154)

* $p<0.05$

ionizing radiation, reactive oxygen species and oestrogen metabolites) associated with breast cancer.

Several studies have been performed to elucidate the role of DNA damage in breast cancer predisposition (Table 1). Patel et al.[28] showed higher frequencies of chromatid gaps/breaks in peripheral blood lymphocytes of breast cancer patients (159.64 ± 13.953) and their first-degree relatives (FDR) (135.89 ± 9.011) compared with control women (91.94 ± 5.901), following *in vitro* G_2 phase X-irradiation. They reported that the risk of FDR developing breast cancer was 2.7 times higher as compared with controls.

Since ionizing radiation is established as an etiologic agent for breast cancer, several studies have used g-irradiation as a source of DNA damage trying to clarify its influence in breast cancer risk. Alapetite et al.[29] hypothesised that sporadic cases of clinical hypersensitivity to radiation treatment in breast cancer cases may be related to DNA repair deficiencies. Because of this, they applied alkaline comet assay to measure the individual DNA repair capacity of *in vitro* g-irradiated lymphocytes from breast cancer patients with severe normal tissue reactions to radiotherapy compared to breast cancer patients with normal responses to treatment as well as healthy donors. They observed that breast cancer patients with unusual severe reactions presented higher DNA damage levels (23.22 ± 8.97) after 1 hour of exposure compared with breast cancer patients without reactions (16.59 ± 4.62) and healthy women (13.98 ± 4.9), and that control patients exhibited a repair capacity in the same range as healthy donors. Buchholz et al.[10] considered phenotype of cellular radiosensitivity defined by a chromatid-break assay, after 4 hours of g-irradiation. They observed higher levels of DNA damage in breast cancer patients with a family history of breast cancer (0.67 ± 0.14) compared to breast cancer patients with a negative family history (0.49 ± 0.25) and healthy women (0.45 ± 0.14). A more recent study[27] reported DNA damage frequencies in breast cancer patients and healthy women before, immediately after and 10 minutes after exposure to g-irradiation. The results showed higher DNA damage levels (mean comet tail moments) in breast cancer cases compared to controls in all the times mentioned (10.78 ± 3.63 and 6.86 ± 2.76, before irradiation; 21.24 ± 4.88 and 14.97 ± 4.18, immediately after irradiation; and 14.76 ± 5.35 and 9.75 ± 3.35, 10 minutes after exposure, respectively). They also showed that DNA damage was associated with breast cancer risk.

Other types of mutagens have been used to indirect measurement of DNA repair capacity, such as bleomycin, doxorubicin and N-methyl N-nitro N-nitrosoguanidine (MNNG). Jyothish et al[9] quantified cromatid breaks after DNA damage induced by bleomycin in lymphocytes of breast cancer patients with family history, their relatives, breast cancer patients with negative family history

and healthy women. Breast cancer patients (1.2819 ± 0.443) with a positive family history, their relatives (0.7935 ± 0.215) and sporadic breast cancer patients (0.8189 ± 0.179) presented higher cromatid break frequencies compared with controls (0.580 ± 0.200). Another study[30] measured DNA damage, by alkaline comet assay, at basal DNA damage, after treatment with MNNG and 2 hours of treatment to study repair efficiency in breast cancer patients, their FDR and control women. They observed an increased in DNA damage levels (basal, after treatment and after allowing repair) from controls to FDR and to breast cancer patients and from FDR to breast cancer patients. On the other hand, Blasiak et al.[31] evaluate the removal of DNA damage induced by hydrogen peroxide and doxorubicin before and during/after chemotherapy in the lymphocytes of breast cancer patients and controls, by alkaline comet assay. Breast cancer patients exhibited higher DNA damage levels when exposed to hydrogen peroxide and doxorubicin than controls, both before and after chemotherapy.

Another type of DNA damage observed in breast tumour and nontumour tissue is the bulky DNA adducts, produced by a wide range of chemical, such as polycylic aromatic amines and benzo(a)pyrene, present in cigarette smoking, the ambient air and various foods.[32,33] Rundle et al.[33] designed a case-control study to analyse PAH-DNA adducts in tumours and nontumours breast tissue from cases and benign tissue from controls. They observed mean adduct levels significantly higher for the tumour tissue samples (0.47 ± 0.30) compared with benign tissue samples (0.38 ± 0.19). Furthermore, DNA adduct levels were significantly associated with breast cancer risk. Santella group's have developed some studies[34,32] concerning DNA repair capacity of lymphoblastoid cell lines from breast cancer patients compared with non-affected sisters, using benzo(a)pyrene diol epoxide (BPDE) as a test mutagen. In both studies, poorer DNA repair capacity was observed in case patients compared with control individuals (non-affected sisters).

In conclusion, all these findings corroborate the important and crucial involvement of DNA damage, and, in consequence, all the cellular mechanisms triggered by it (such as DNA damage recognition and signalling and DNA repair pathways), in breast cancer susceptibility.

DNA damage signalling and DNA repair gene polymorphisms, DNA repair capacity and breast cancer risk

Low-penetrance susceptibility alleles are defined as polymorphic genes with specific alleles associated with an altered risk for disease susceptibility. Usually, the variants in these genes are common in the general population. Therefore, although each variant may be associated with a small risk increase for breast cancer in an individual, the risk attributable in the population as a whole is likely to be higher than for rare, high-penetrance susceptibility genes. Several reports have demonstrated the importance of polymorphisms in several cellular mechanisms on breast cancer susceptibility.[35-44]

The DNA damage signalling and repair pathways are mechanisms essential to the viability of the genome. The important role of DNA repair in the maintenance of a normal cellular genotype and a cancer-free state is obvious in family history cancer, in which the presence of rare but highly penetrating variant alleles at a number of loci is associated with a high risk of cancer. A classic example is *xeroderma pigmentosum*, a prototype cancer gene syndrome associated with the development of UV-induced skin cancers resulting from the loss of function of a gene of the NER pathway.[13] Other genes with direct or indirect roles in DNA repair and in which variant alleles are associated with elevated cancer risk, include *BRCA1*, *BRCA2*, *TP53*, *ATM*, and *NBS1*.[12] A huge number of common polymorphisms have been described in DNA damage signalling and repair genes.[45-47] Observations of inter-individual differences in measures of DNA damage suggest that these polymorphisms may alter the functional properties of DNA repair enzymes. For all the evidences, it seems of great importance to define the meaning of DNA damage signalling and repair polymorphisms in the context of protein and pathway functions and their contribution to breast cancer risk.

In the points below, we will focus on studies comprising association of polymorphisms in BER, NER, DBSR and DNA damage signalling genes with both breast cancer susceptibility and DNA repair capacity.

BER polymorphisms

Base excision repair pathway is the main mechanism to repair DNA damage of endogenous origin, mainly oxidation of DNA by reactive oxygen species generated by a wide range of normal metabolism and spontaneous deamination of DNA bases, and of exogenous origin, including ionising radiation and long-wave UV light, as already mentioned.[48] Several *BER* genes have been described to present polymorphic regions, namely, *APE1, XRCC1,* glycosylases *(OGG1, MTH1, MYH), LIG1* and *LIG3.*[47] Several works have been conducted with the aim of determining the influence of BER polymorphisms in risk of developing cancer,[49-51] namely in breast cancer (Table 2).

The 8-oxoguanine DNA glycosylase (OGG1) is a protein from the family of glycosylase responsible for the excision of a modified base, in this case 8-oxoguanine (8-OH-G), from DNA that has been damaged. The most common polymorphism found in *OGG1* gene is *Ser326Cys*, resulting in an amino acid substitution, which seems to induce reduction of the activity for excision of 8-OH-G.[52] Association of *Ser326Cys* polymorphism in *OGG1* with breast cancer was assessed in 2 studies,[53,54] but no influence was observed in both reports.

XRCC1 protein is thought to act as scaffold protein for both single-strand break repair and base excision repair activities.[55] It has been shown that XRCC1 interacts with DNA Polb, DNA LigIII

Table 2 – Studies of association of BER polymorphisms with breast cancer risk and functional phenotype

Gene Name	Polymorphism Name	Variant frequency Cases	Controls	Breast cancer risk (OR; 95% CI)	DNA repair capacity/ environment interaction	Reference
OGG1	*Ser326Cys*	0.225	0.240	0.98 (0.52-1.86)	*	Vogel et al. 2003[54]
		0.469	0.497	1.3 (0.92-1.93)	*	Choi et al. 2003[53]
XRCC1	*Arg194Trp*	0.05	0.07	0.7 (0.4-1.3)	No	Duell et al. 2001[59]
	Arg399Gln	0.35	0.36	1.0 (0.8-1.4)	Yes	
	Arg194Trp	0.071	0.069	1.03 (0.62-1.67)	No	Moullan et al. 2003[60]
	Arg280His	0.081	0.068	1.80 (1.07-3.05)	No	
	Arg399Gln	0.348	0.359	0.95 (0.74-1.23)	No	
	Arg194Trp	0.086[a)]	0.041[a)]	2.24 (0.91-5.53)[c)]		
		0.056[b)]	0.070[b)]	2.46 (0.98-6.17)[d)]	*	
				1.58 (0.39-6.39)[e)]		Smith et al. 2003[61]
	Arg399Gln	0.299[a)]	0.361[a)]	0.92 (0.53-1.58)[c)]		(DR3)
		0.296[b)]	0.368[b)]	0.57 (0.32-1.02)[d)]	*	
				0.74 (0.31-1.72)[e)]		
	Arg194Trp	0.08	0.05	1.60 (0.89-2.87)	*	Smith et al. 2003[63]
	Arg399Gln	0.36	0.34	1.03 (0.71-1.49)	*	
	Arg399Gln	0.281	0.273	1.20 (0.85-1.69)	Yes	Shu et al. 2003[64]
	Arg194Trp	0.056	0.066	0.79 (0.60-1.04)	Yes	Han et al. 2003[65]
	Arg399Gln	0.370	0.362	1.03 (0.77-1.37)	No	
	Gln632Gln	0.408	0.422	0.90 (0.69-1.16)	No	
	Arg194Trp	0.034	0.027	1.26 (0.58-2.72)	*	Forsti et al. 2004[67]
	Arg399Gln	0.321	0.320	1.00 (0.76-1.31)	*	
	Arg399Gln	0.367[a)]	0.360[a)]	**	Yes	Figueiredo et al. 2004[62]
		0.331[b)]	0.486[b)]	**		
	Arg194Trp	0.039	0.053	0.48 (0.19-1.17)	*	Deligezer et al. 2004[66]
	Arg399Gln	0.397	0.374	0.97 (0.60-1.56)	*	
	Arg194Trp	0.215	0.093	2.04 (1.12-3.72)	*	Chacko et al. 2005[68]
	Arg280His	0.114	0.108	0.62 (0.33-1.12)	*	
	Arg399Gln	0.341	0.159	2.18 (1.30-3.66)	*	
	Arg194Trp	0.061	0.067	0.78 (0.50-1.20)	Yes	Shen et al. 2005[69]
	Arg399Gln	0.361	0.359	1.23 (0.91-1.66)	Yes	
	Arg399Gln	0.354[a)]	0.403[a)]	0.66 (0.40-1.06)[d)]	*	Costa et al, unpublished
		0.401[b)]		1.03 (0.58-1.83)[e)]		

* Study not realized; ** visualized in the test; a) without FH; b) with FH; c) variant genotypes vs wild type genotype between healthy women with FH vs healthy women without FH; d) variant genotypes vs wild type genotype between breast cancer patients without FH vs healthy women without FH; e) variant genotypes vs wild type genotype between breast cancer patients with FH vs healthy women without FH.

and APE1, through a BRCT (BRCA C-terminal domain) domain at the C-terminus.[56] XRCC1 seems to be essential to mammalian viability, since disruption of it in mice leads to embryonic lethality.[57] Several polymorphisms have been found in *XRCC1* gene and some have been linked with a variety of cancers.[51] Three of these polymorphisms have been largely investigated in breast cancer: *Arg194Trp, Arg280His* and *Arg399Gln* (Table 2). Hu et al.[58] have demonstrated that breast cancer patients with *XRCC1 Arg399Gln* and/or *APE Asp148Glu* polymorphisms are associated with cell-cycle delay in response to ionizing radiation. Duell et al.[59] observed a higher risk for radiation exposure among women with *Arg399Arg* genotype (OR= 3.3; 95% CI 1.2-9.4). However, no association was found regarding breast cancer risk. A more recent study[60] reported no association of breast cancer risk and *XRCC1 Arg194Trp* and *Arg399Gln* polymorphisms (OR=1.03; 95% CI 0.62-1.67; OR=1.80; 95% CI 1.07-3.05, respectively). Moreover, they reported a positive association between *280His* allele and increased breast cancer risk (OR=1.80 95% CI 1.04-3.08). This association was seen in both radiation-sensitive and non- non-radiation-sensitive patients, indicating that the association was with breast cancer status and not the radiation sensitivity seen in some patients. They also found that combination of *194Trp* and *399Gln* alleles are associated with development of adverse reactions to radiotherapy (OR=4.33; 95% CI 1.24-15.12). Smith et al.[61] compared breast cancer patients with and without FH and healthy ones with a positive FH to healthy women with negative FH. Their results did not support association of *XRCC1 Arg194Trp* and *Arg399Gln* polymorphisms with breast cancer risk. However, they observed an interaction between *XRCC1 Trp194* allele and *XRCC3 241Met* allele in breast cancer risk (OR=8.74; 95% CI 1.13-67.53). Another report, by Figueiredo et al.,[62] investigating effects of *XRCC1 Arg399Gln* polymorphism and FH on breast cancer risk have showed association of *Arg399Arg* and *Arg399Gln* genotypes and breast cancer susceptibility in positive FH women (OR=2.92 95% CI 1.47-5.79; OR=3.85 95% CI 1.94-7.62, respectively) when compared with *Arg399Arg* genotype of negative FH women. Moreover, these genotypes are associated with one-half breast cancer risk in women with body mass index (BMI) >25Kg/m^2 compared with women presenting BMI within normal limits. We performed a case-control study, including 71 breast cancer patients with and 219 without FH and 340 healthy women with negative FH, investigating *XRCC1 Arg399Gln* polymorphism. We observed a lower frequency of *399Gln* genotypes in breast cancer patients with negative FH (56.2%) compared with controls (65.7%). These results suggest a protective effect of *399Gln* genotypes on breast cancer in women without FH (OR=0.66 95% CI 0.40-1.06; OR adjusted for age by logistic regression). The protective effect of *399Gln* genotypes could be explained by two hypotheses. First, the gene variants could independently confer improved function to XRCC1 protein. Secondly, these variants could diminish the efficiency of the protein but still provide decreased cancer risk, for in the presence of excessive oxidative damage, cells carriers of these variants would have decreased ability to repair and might be more likely to undergo apoptosis. Another study from Smith et al.,[63] comparing breast cancer patients and normal individuals, showed the same results, alone *XRCC1 Arg194Trp* and *Arg399Gln* polymorphisms were not associated with breast cancer development, being associated only when combined with other polymorphisms. The inexistent association of *XRCC1 Arg399Gln* with breast cancer susceptibility was confirmed by another report[64] done with a broader sample (1088 cases and 1182 controls). However, a 3.27-fold increase of risk of menopausal women who had a higher level of sex hormone-binding globulin was found. Han et al.[65] have also found no association of *XRCC1 Arg194Trp, Arg399Gln* and *Gln632Gln* polymorphisms and breast cancer risk, using a large case-control sample (998 cases and 1369 controls). They observed that *194Trp* haplotype carriers present a marginal decrease in breast cancer risk (OR=0.79 95% CI 0.60-1.04) and no significant association with cigarette smoking. Furthermore, they reported an interaction between higher plasma carotene levels and *194Trp* haplotype carriers with decreased risk to breast cancer. In a Finish and a Turkish studies, the *XRCC1 Arg194Trp* and *Arg399Gln* polymorphisms are not associated with breast cancer risk.[66,67] In contrast, in an Indian population,[68] *XRCC1 Arg194Trp* and *Arg399Gln* polymorphisms seems to be associated to breast cancer susceptibility.

They also analysed *XRCC1 Arg280His* polymorphism, and they only observed an interaction in post-menopausal women (OR=0.26 95% CI 0.1-0.66). A recent work from Shen et al.[69] showed no association of *XRCC1 Arg194Trp* and *Arg399Gln* polymorphisms with breast cancer. They also evaluated the interaction between *XRCC1* polymorphisms and PAH-DNA adducts, intake of fruits and vegetables in breast cancer risk. Their results suggest different effects of the 2 polymorphisms in combination with the environmental/dietary referred, probably due to altered affinity of *XRCC1* for its BER partners, attributed to different polymorphisms status, leading to different gene-exposure interaction patterns.

NER polymorphisms

The Nucleotide Excision Repair (NER) is the most versatile and flexible DNA repair pathway and it removes a wide range of lesions, including UV-induced photoproducts, bulky adducts, cross-links and oxidative damage.[20,70] Until today, more than 200 polymorphisms have been identified in the NER pathway[46,47] and several studies have been performed to associate NER polymorphisms and cancer risk.[71-74] In table 3 we show studies associating breast cancer susceptibility and NER polymorphisms.

Two recent studies[75,67] have analysed a frequent polymorphism in *XPC* gene, *Lys939Gln.* The XPC protein forms a complex with HR23B protein, XPC-HR23B complex, being responsible for initiation of the NER pathway through sensing and binding on lesions, distortion of DNA double helix and necessary for recruitment of all subsequent NER factors.[76] Försti et al.[67] have performed a case-control study in Finish and Polish populations. They observed a significantly higher frequency of heterozygote genotype in breast cancer cases compared with controls (46.2%

Table 3 – Studies of association of NER polymorphisms with breast cancer risk and functional phenotype

Gene Name	Polymorphism Name	Variant frequency Cases	Controls	Breast cancer risk (OR; 95% CI)	DNA repair capacity/ environment interaction	Reference
XPC	*Lys939Gln*	0.320	0.297	1.12 (0.91-1.23)	*	Försti et al. 2004[67]
		0.325	0.300	1.12 (0.91-1.23)	*	Zhang et al. 2005[75]
XPG	*Asp1104His*	0.29	0.23	1.33 (1.00-1.78)	No	Kumar et al. 2003[82]
XPD	*Asp312Asn*	0.25	0.21	1.58 (0.85-2.95)[a)]	Yes	Tang et al. 2002[89]
	Lys751Gln	0.36	0.36	1.02 (0.45-2.29)[b)]	Yes	
	Asp312Asn	0.34[c)]	0.39[c)]	0.80 (0.62-1.04)	*	Försti et al. 2004[67]
		0.42[d)]	0.39[d)]			
	Lys751Gln	0.41	0.41	0.98 (0.76-1.27)	*	
	Asp312Asn	0.35	0.25	2.01 (1.03-3.94)[a)]	Yes	Shi et al. 2004[90]
	Lys751Gln	0.34	0.30	1.19 (0.62-2.32)[a)]	Yes	
	Asp312Asn	0.24	0.34	2.06 (1.39-3.07)[b)]	*	Justenhoven et al. 2004[91]
	Lys751Gln	0.39	0.36	1.32 (0.94-1.86)[b)]	*	
	Lys751Gln	0.39	0.36	1.21 (1.01-1.44)[a)]	Yes	Terry et al. 2004[92]
	Asp312Asn	0.05	0.05	1.10 (0.72-1.75)	*	Lee et al. 2005[93]
	Asp312Asn	0.36[e)]	0.33[e)]	1.38 (1.11-1.73)[b)]	*	Kuschel et al. 2005[94]
	Lys751Gln	0.37[e)]	0.37[e)]	1.01 (0.82-1.25)[b)]	*	
	Asp312Asn	0.34[f)]	0.34[f)]	10.2 (0.77-1.36)[b)]	*	
	Asp312Asn	0.38[g)]	0.41[g)]	0.77 (0.54-1.10)[b)]	*	
	Lys751Gln	0.32[h)]	0.33	0.63 (0.23-1.72)[b)h)]	*	Costa et al. 2005 (unpublished)
		0.34[i)]		1.04 (0.59-1.84)[b)i)]		
ERCC1	*3'UTR C8092A*	0.26	0.28	0.58 (0.38-0.89)[j)]	No	Lee et al. 2005[97]
	C354T	0.50	0.50	1.08 (0.84-1.39)[a)c)]	Yes	
XPF	*Arg415Gln*	0.08	0.06	-[c)]	*	Smith et al. 2003[63]
	T835C	0.25	0.23	1.20 (0.87-1.62)	*	Lee et al. 2005[93]

* Study not realized; a) Variant genotypes vs wild type genotype between breast cancer patients vs healthy women; b) homozygotes variant genotype vs wild type genotype between breast cancer patients vs healthy; c) Finish population; d) Polish population; e) UK population; f) Australia population; g) Heidelberg population; h) breast cancer patients with FH; i) breast cancer patients without FH; j) homozygote variant genotype vs wild type and heterozygote genotypes between breast cancer patients vs healthy women.

and 36.5%, respectively) in the Finish population. However, they found control group deviations from Hardy-Weinberg equilibrium, and the observed differences could be the result of it. In the Polish population, no association of *XPC Lys939Gln* polymorphism and breast cancer risk was found compared family-history breast cancer patients and control women (OR=0.78 95% CI 0.57-1.00). Contrasting results were obtained by Zhang et al.[75] in a Chinese population. They reported a heterozygote genotype frequency statistically different between breast cancer cases and controls (46.8% and 36.8%, respectively) and carriers of this genotype had an increased risk for breast cancer ($p<0.05$; OR=1.47 95% CI 1.00-2.16).

XPG is an endonuclease essential for the two incisions steps in NER pathway, catalyzing incision at approximately 5 nucleotides 3′ from the site of damage and also involved non-enzymatically in the subsequent 5′ incision.[77] One common *XPG* polymorphism has been described, *Asp1104His,* and some case-control studies have been presented.[78-81] In breast cancer, only one study has been performed by Kumar et al.[82] They observed a significantly increase in the combined frequency of heterozygote and homozygote genotypes in cases compared to controls ($p=0.03$). The presence of the variant seems to increase breast cancer susceptibility (OR=1.50 95% CI 1.04-2.16). Furthermore, they carried out a measurement of repair kinetics of cyclobutane pyrimidines dimmers and tried to correlate it with the *XPG Asp1104His* polymorphism, but did not find any significantly difference.

XPD is a highly polymorphic gene and correlation of their polymorphism and cancer risk have been studied intensively.[71,72,83] XPD protein is a subunit of the TFIIH complex and has important roles in transcription and NER pathway. It participates in the local unwind of DNA helix to permit RNA transcription machinery access the promoter and the NER machinery access the lesion.[20] Two common *XPD* polymorphisms have been associated with a differential DNA repair capacity.[84-88] Several studies have tried to clarify the real meaning of *XPD* polymorphisms and breast cancer susceptibility, some of them related to environmental/life style factors. Tang et al.[89] study did not suggest that *XPD Asp312Asn* and *Lys751Gln* polymorphisms are associated with breast cancer, although they did find that presence of one or two *Asn312* allele and *Gln751Gln* genotype is significantly associated with elevated levels of PAH-adducts in tumor tissue from breast cancer patients compared with benign tissue. A study using a broader sample was performed by Försti et al.,[67] in a Finish and a Polish population. They observed that only *XPD Asn312Asn* genotype frequency are significantly different between Finish breast cancer patients and controls ($p=0.02$). This genotype seems to grant a protective effect to their carriers (OR=0.51 95% CI 0.27-0.94). No associations were found on *XPD Lys751Gln* polymorphism in the Finish population and in both polymorphisms in the Polish population. Shi et al.[90] showed an association of breast cancer with variant *312Asn* genotypes (OR=2.01 95% CI 1.03-3.94), in contrast to *Lys751Gln* polymorphism. They observed genotype-phenotype correlations among control group: *312Asn* and *751Gln* variant genotypes exhibited lower DNA repair capacity than the wild type genotype. A study performed in a German population,[91] using a broader sample, showed contrary results comparing with earlier study. *XPD Asp312Asp* genotype carriers presented a higher risk to breast cancer (OR=2.06 95% CI 1.39-3.07). Furthermore, this risk was more relevant when women were carriers of combined *XPD Asp312Asp* and *Gln751Gln* genotypes (OR=3.49 95% CI 2.30-5.28). Terry et al.[92] found a modest, statistically significant association between those subjects with at least one variant *XPD Gln751* allele and breast cancer risk (OR= 1.21 95% CI 1.01-1.44). Moreover, they observed that both *Gln751Gln* genotype and PAH-DNA adducts above the median was associated with a higher increased risk to breast cancer (OR= 1.9 95% CI 1.15-3.15) versus those with non-detectable adducts and *Lys751Lys* genotype. A study performed in an Asian population,[93] showed no association with *XPD Asp312Asn* polymorphism. However, carriers of combined *XPD Asn312* allele and another polymorphism in a NER gene (*XPF Ser835Ser*) showed a three-fold increased risk of breast cancer (OR=2.6 95% CI 1.02-6.48). A vast case-control study was performed in three populations: United Kingdom (UK), Australia and Heidelberg.[94] They first analysed *XPD Asp312Asn* and *Lys751Gln*

polymorphisms in the UK population, and found a positive association of *Asp312Asn* polymorphism with breast cancer, and so they genotyped other two populations for this polymorphism. However, the result was not reproduced. A very recent work, by Metsola et al,[78] showed no statistically significant differences in the frequency of *XPD Lys751Gln* genotypes between cases and controls (OR=1.10 95% CI 0.74-1.63). They also studied association between this polymorphism and breast cancer risk regarding smoking habits. They observed an increased risk for women who had smoked more than 5 pack for year with the *XPD Lys751Gln* genotype (OR=4.41 95% CI 1.62-12.0). We performed a case-control study, including 74 breast cancer patients with and 203 without FH and 348 healthy women with negative FH, investigating *XPD Lys751Gln* polymorphism. As observed in previous studies, we did not find any statistical significant association between the 2 firsts groups and any of the genotypes compared with healthy women (Table 3).

The action of two endonucleases, ERCC1-XPF, is important to the incisions at both sides and few nucleotides away from the lesion[76]. Some polymorphisms have been described in *XPF* and *ERCC1* genes.[46,95,96] Just one study[97] analysed 2 *ERCC1* polymorphisms, *3'UTR C8092A* and *C354T*, and breast cancer risk. Lee et al found a protective effect of *8092AA* genotype to breast cancer (OR=0.58 95% CI 0.38-0.89). Furthermore, when cases were divided into subgroups by ER/PR status, they observed an 2-fold increased risk of breast cancer in women carriers of *ERCC1 354CT* or *354TT* genotypes and negative expression of oestrogen and progesterone receptors (OR=1.99 95% CI 1.35-2.94). Smith et al.[63] analysed *XPF Arg415Gln* polymorphism and found an increased frequency of *Gln415Gln* in breast cancer cases compared with controls.

DSBR polymorphisms

Double-strand break (DSB) is the most dangerous type of DNA damage cells can undergo. DSB could result from exogenous agents, such as ionizing radiation and certain chemotherapeutic agents, of endogenous origin, for instance reactive oxygen species, mechanical stress on chromosomes and replication errors.[15] Several genes described as breast cancer susceptibility genes are important DSBR genes and for DSBR pathway, such as *BRCA1, BRCA2, ATM, P53* and *CHK2*.[15] Cells evolved 2 pathways to repair this type of lesions: NHEJ and HR. Some polymorphisms have been demonstrated in some of NHEJ and HR genes.[45,98,99] Several of these have been examined in case-control studies of breast cancer risk (Table 4).

NBS1 protein is part of the complex MRE11-Rad50-NBS1, and play critical roles in DNA repair and cell cycle checkpoint activation.[100] Mutations in *NBS1* gene result in a known syndrome, Nijmegen breakage syndrome (NBS). Cells from NBS patients exhibit gamma-irradiation sensitivity, S-phase checkpoint defects, and genomic instability. Three studies showed no significant association of *NBS1 Glu185Gln* polymorphism and breast cancer risk.[45,67,75]

RAD51 is a protein participating in DSBR pathway that forms a heterodimer with several genes (such as *XRCC2, XRCC3, BRCA2*) playing an important role in DSBR by HR.[101] The majority of *RAD51* polymorphisms described are in untranslated regions (UTR). Kuschel et al.[45] analysed *RAD51 5'UTR G135C* and *5'UTR G172T* polymorphisms in 1440 breast cancer patients and 960 healthy women. They did not find any significant difference in genotype frequencies between cases and controls. Another study, by Webb et al.,[102] evaluated *RAD51 5'UTR G135C* genotype frequencies, in 1295 breast cancer patients and 650 controls. Their data were similar to those found by Kuschel et al,[45] providing no evidence of correlation of breast cancer risk and this polymorphism (OR=1.08 95% CI 0.84-1.41). These results were corroborated in an Asian population by Lee et al.[97] They demonstrated no association of breast cancer susceptibility to *RAD51 5'UTR G135C* and *5'UTR G172T* polymorphisms. We performed a case-control study, including 75 breast cancer patients with FH and 186 without FH and 339 healthy women with negative FH, investigating *RAD51 5'UTR G135C* polymorphism. We did not find any statistical significant association of sporadic breast cancer risk and this polymorphism (Table 4). However, we observed an increased risk to breast cancer in women carriers of *GC135* or *CC135* genotypes presenting a positive FH of breast cancer (OR=2.15 95% CI 1.12-4.10). Several studies

Table 4 – Studies of association of DSBR polymorphisms with breast cancer risk

Gene Name	Polymorphism Name	Variant frequency Cases	Controls	Breast cancer risk (OR; 95% CI)	Reference
NBS1	*Glu185Gln*	0.34	0.32	1.18 (0.85-1.64)[a]	Kuschel et al. 2002[45]
		0.36	0.39	0.89 (0.68-1.15)[a]	Försti et al. 2004[67]
		0.36	0.38	0.89 (0.68-1.15)[a]	Zhang et al. 2005[75]
RAD51	*5'UTR G135C*	0.07	0.07	2.50 (0.60-10.9)[a]	Kuschel et al. 2002[45]
	5'UTR G172T	0.43	0.44	0.90 (0.70-1.20)[a]	
	5'UTR G135C	0.08	0.07	1.08 (0.84-1.41)	Webb et al. 2005[102]
	5'UTR G135C	0.13	0.13	0.89 (0.67-1.17)[b]	Lee et al. 2005[97]
	5'UTR G172T	0.05	0.05	0.84 (0.56-1.26)[b]	
	5'UTR G135C	0.11[c]	0.06	2.15 (1.12-4.10)[b][c]	Costa et al. 2005
		0.09[d]		1.46 (0.87-2.46)[b][d]	(unpublished)
RAD52	*3'UTR C2259T*	0.46	0.46	1.00 (0.90-1.20)[b]	Kuschel et al. 2002[45]
	Ser346ter	0.01	0.01	0.97 (0.43-2.21)[b]	Han et al. 2002[108]
	3'UTR C2259T	0.58	0.53	1.33 (1.02-1.75)[b]	Lee et al. 2005[97]
XRCC2	*5'UTR G4234C*	0.22	0.24	1.00 (0.70-1.30)[a]	Kuschel et al. 2002[45]
	Arg188His	0.08	0.08	2.60 (1.00-6.70)[a]	
	3'UTR C41657T	0.06	0.06	0.40 (0.10-1.30)[a]	
	Arg188His	0.09	0.06	1.52 (1.04-2.22)[b]	Rafii et al. 2002[110]
	Arg188His	0.08	0.07	1.12 (0.88-1.44)[b]	Han et al. 2004[104]
	Arg188His	0.07	0.08	1.01 (0.77-1.33)[b]	Webb et al. 2005[102]
XRCC3	*5'UTR A4541G*	0.20	0.19	0.90 (0.70-1.30)[a]	Kuschel et al. 2002[45]
	IVS5-14 A>G	0.32	0.34	0.80 (0.60-1.00)[a]	
	Thr241Met	0.40	0.36	1.30 (1.10-1.60)[a]	
	Thr241Met	0.43[d]	0.39	1.06 (0.59-1.91)[b][d]	
		0.37[c]		0.95 (0.40-2.26)[b][c]	Smith et al. 2003[61]
	Thr241Met	0.41	0.37	0.98 (0.67-1.41)[b]	Smith et al. 2003[63]
	Thr241Met	0.32[e]	0.28[e]	1.28 (0.97-1.69)[e]	
		0.33[f]	0.34[f]	0.97 (0.71-1.33)[f]	Försti et al. 2004[67]
	5'UTR A4541G	0.20	0.18	1.10 (1.00-1.20)[b]	Han et al. 2004[111]
	IVS5-14 A>G	0.32	0.31	1.04 (0.87-1.25) [b]	
	Thr241Met	0.37	0.38	0.92 (0.76-1.11) [b]	
	Thr241Met	0.42	0.39	1.47 (1.00-2.15)[b]	Figueiredo et al. 2004[62]
	Thr241Met	0.36	0.38	0.84 (0.64-1.09)[b]	Webb et al. 2005[102]
	Thr241Met	0.33	0.28	1.79 (0.98-3.26)[a]	Zhang et al. 2005[75]
	Thr241Met	0.34[c]	0.33	1.05 (0.51-2.17)[c]	Costa et al. 2005
		0.39[d]		1.41 (0.83-2.40)[d]	(unpublished)
BRCA2	*Asn372His*	0.29	0.26	1.46 (1.03-2.07)[a]	Spurdle et al. 2002[114]
	Asn372His	0.19	0.20	1.65 (0.36-7.58)[a]	Ishitobi et al. 2003[115]
	Met784Val	0.10	0.06	2.03 (1.07-3.87)[b]	
	Thr1915Met	0.04[g]	0.03	2.20 (0.20-23.7)[a][g]	Górski et al. 2005[116]
		0.03[h]		5.40 (1.20-24.6)[a][h]	
Ku70	*G1796T*	0.37	0.36	2.50 (0.60-10.9)[a]	Kuschel et al. 2002[45]
	C-61G	0.06	0.17	*	
	G1796T	0.25	0.28	*	
	A46922G	0.05	0.07	*	
Ku80	*G69506A*	0.09	0.06	*	
	G69632A	0.08	0.06	*	Fu et al. 2003[117]
LIG IV	*Ile591Val*	0.02	0.01	*	
	C4026T	0.26	0.27	*	
	C4044T	0.13	0.14	*	
DNA-PK	*C55966T*	0.11	0.11	*	
XRCC4	*A245G*	0.26	0.27	*	
	T1394G	0.10	0.15	*	
	C1475T	0.38	0.33	*	

a) Homozygote variant genotype vs wild type genotype between breast cancer patients vs healthy; b) Variant genotypes vs wild type genotype between breast cancer patients vs healthy women; c) breast cancer patients with FH; d) breast cancer patients without FH; e) Finish population; f) Polish population; g) under age 40 years; h) above age 41 years; * not described in the reference

have showed that *RAD51 135C* variant seems to modulate breast cancer risk among *BRCA1/2* mutation carriers.[103-107]

RAD52 protein interacts and co-localizes with RAD51 *in vivo* facilitating RAD51 activities and binds directly to DSB protecting them from exonuclease activity.[15] Kuschel et al.[45] identified *RAD52 3'UTR C2259T* polymorphism and did not observe any association to breast cancer risk (OR=1.0 95% CI 0.9-1.2). Divergent results were obtained by Lee et al.,[97] in an Asian population. They reported borderline association between *RAD52 3'UTR C2259T* polymorphism and breast cancer risk (OR=1.02 95% CI 1.02-1.75). Another stop codon *RAD52* polymorphism, *Ser346ter*, was analysed by Han et al.[108] They did not find any statistical significant difference in genotype *Thr241Met* polymorphism to breast cancer risk in gene-gene interaction, with *XRCC1 Arg194Trp* (OR=8.74 95% CI 1.13-67.53). They presented similar results in another study including a broader sample and other polymorphisms.[63] Försti et al.[67] did not find association of breast cancer risk to *XRCC3 Thr241Met* polymorphism, neither in a Finish nor in a Polish population (OR= 1.28 95% CI 0.97-1.69; OR=0.97 95% CI 0.71-1.33, respectively). Han et al.[111] showed a borderline significantly increased risk of breast cancer (OR= 1.10 95% CI 1.0-1.2) and no associations between *IVS5-14 A>G* and *Thr241Met* polymorphisms and breast cancer risk. Figueiredo et al.[62] found a marginal increase in breast cancer risk of *XRCC3 Met241Met* genotype carriers (OR=1.47 95% CI 1.00-2.15). Moreover, they observed some evidence for a combined effect of body mass index and *XRCC3 241Met* on estimates of risk and no relation when considered FH. Another study, by Webb et al.,[102] failed to associate breast cancer risk with *XRCC3 Thr241Met* polymorphism (0.84 95% CI 0.64-1.09). A study performed in an Asian population[75] showed a slight higher increase in breast cancer in women carriers of *XRCC3 Met241Met* genotype. We analysed *XRCC3 Thr241Met* polymorphism in 74 breast cancer patients with FH and 176 without FH and 341 healthy women with negative FH. We also did not find any statistically significant difference in genotypes frequencies between breast cancer patients with and without FH and control group (Table 4).

Mutations in *BRCA2* gene have been described as being associated with hereditary breast cancer. However, the risk of developing cancer is not identical for all carriers of *BRCA2* mutations, being also influenced by allelic heterogeneity, low-penetrance genes and environmental/hormonal cofactors. It is known that BRCA2 protein is involved in HR pathway and interacts directly with RAD51, being essential for the formation of RAD51 foci after damage[22]. Some polymorphisms have been described in *BRCA2* gene (http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/BIC). Healey et al.[113] study several *BRCA2* polymorphisms (*a-26g, Asn298His, Asn372His, Thr1915Met* and *Arg2034Cys).* They found association with breast cancer risk only in homozygote variant carriers (OR=1.31 95% CI 1.09-1.58). Similar results were *BRCA2 His372His* genotype was associated with increased breast cancer risk in non-carrier *BRCA1/2* mutations. Ishitobi et al.[115] performed a case-control study in a Japanese population analysing two *BRCA2* polymorphisms: *Asn372His* and *Met784Val*. They showed that *784Val* variant carriers have a significantly increased risk of breast cancer (OR=2.03 95% CI 1.07-3.87) after adjustment for the classical epidemiological risk factors. Moreover, this variant was also correlated with a poor prognosis. On the other hand, *Asn372His* not seemed to be associated with breast cancer risk. Górski et al.[116] showed that heterozygote state of *Thr1915Met* polymorphism was associated with early onset breast cancer (OR=1.4 95% CI 1.0-2.0), but the homozygote variant was associated with later onset breast cancer (OR=5.4 95% CI 1.2-24.6).

In NHEJ pathway, the heterodimer formed by Ku70 and Ku80, is important to rely on DNA DSB and as a DNA targeting subunit of DNA-dependent protein kinase (DNA-PK)[15,112]. Polymorphisms in these genes are not very common. Kuschel et al.[45] identified synonymous polymorphism in *Ku70: G1796T*. They did not observe any statistical difference in genotype frequencies between breast cancer cases and controls. Fu et al.[117] performed a case-control study in several genes of NHEJ pathway (Table 4). Their results only showed correlation to breast cancer risk of *Ku70 C-61G* and *XRCC4 T1394G* polymorphisms and suggested that the possibility of manifesting tumorigenic phenotype depends on the interaction between genotypic polymorphisms of NHEJ genes (OR=1.46 95% CI 1.19-1.80).

DNA damage signalling polymorphisms

As we mentioned, cells respond to DNA lesions through the actions of systems that detect DNA damage and then trigger various downstream events. ATM encodes a protein kinase, which directly phosphorilate P53 and interacts with molecules in cell signalling in gene are responsible for Ataxia telangiectasia disease, where the affected individuals suffer from severe clinical phenotype, such as extreme radiosensitivity. Some polymorphisms have been described[119] (Table 5). Bretsky et al.[120] screened *ATM* gene in different ethnic groups and found several polymorphisms. *Asp126Glu, Leu546Val* and *Asp1856Asn* are common polymorphisms in both breast cancer patients and controls. No statistical significant differences were observed. Another study screening *ATM* gene was performed by Angéle et al.[121] From the most common polymorphisms identified, they observed an increased risk of breast cancer in women carriers of homozygote variant of the *IVS22-77 T>C* and *IVS48+238 C>G* polymorphisms. Another work, by Tamimi et al,[12], did not find any association between some *ATM* polymorphisms and breast cancer risk, even when considered predicted *ATM* haplotypes. A recent study, by Lee et al.,[123] performed in an Asian population, showed an increased breast cancer risk associated with some *ATM* polymorphisms and with some specific *ATM* haplotypes.

Another important gene in DNA signalling is *BRCA1,* existing as part of the BRCA1-associated genome-surveillance complex, which include NBS1 protein and ATM.[22] Some *BRCA1* polymorphisms have been described and some studies evaluated *BRCA1* haplotypes in breast cancer patients and controls.[124,125] Cox et al.[124] found a modestly positive association between a *BRCA1* haplotype and breast cancer among White women. However, Freedman et al.[125] did not find any evidence for a significant role in sporadic breast cancer of a common *BRCA1* variation.

The P53 protein is a tumour suppressor gene with a pivotal role in the cellular response to a range of stresses induced in the cell.[126,127] The biological end-points of P53 induction are growth arrest or apoptosis. Some common

Table 5 – Studies of association of DNA signalling genetic polymorphisms with breast cancer risk

Gene Name	Polymorphism Name	Variant frequency Cases	Controls	Breast cancer risk (OR; 95% CI)	Reference
ATM	*Asp126Glu*	0.03	0.05	*	Bretsky et al. 2003[120]
	Leu546Val	0.00	0.00	*	
	Asp1856Asn	0.25	0.21	*	
	IVS22-77 T>C	0.40	0.34	1.67 (1.00-2.81)[a)]	Angéle et al. 2003[121]
	IVS48+238 C>G	0.41	0.35	1.66 (1.00-2.76)[a)]	
	G5557A	0.13	0.13	1.07 (0.35-3.24)[a)]	
	-5144 A>T	0.53	0.52	1.13 (0.92-1.39)[b)]	Lee et al. 2005[123]
	IVS21+1049 T>C	0.62	0.59	1.39 (1.09-1.77)[b)]	
	IVS33-55 T>C	0.56	0.54	1.19 (0.96-1.47)[b)]	
	IVS34+60 G>A	0.55	0.53	1.29 (1.04-1.60)[b)]	
	3393 T>G	0.56	0.54	1.24 (1.00-1.54)[b)]	
P53	*16bp duplication Intron3*	*	*	5.30 (1.10-25.6)[b)c)]	Wang-Gohrke et al. 2002[12]
				1.20 (0.90-1.60)[b)d)] [8]	
	Arg72Pro	*	*	2.30 (0.70-7.60)[b)c)]	
				1.10 (0.80-1.40)[b)d)]	
	MspI Intron6	*	*	2.80 (0.80-19.3)[b)c)]	
				1.20 (0.90-1.50)[b)d)]	
	Arg72Pro	0.43	0.35	2.14 (1.21-3.79)[a)]	Huang et al. 2003[133]
	16bp duplication Intron3	0.25[c)]	0.17	4.54 (1.69 -12.5)[a)c]	
		0.21[d)]		1.89 (0.77-4.54)[a)d)]	Costa et al. 2005
	Arg72Pro	0.28[c)]	0.25	1.72 (0.70-4.17)[a)c)]	(unpublished)
		0.26[d)]		1.25 (0.61-2.56)[a)d)]	

* Not described in the reference; a) Homozygote variant genotype vs wild type genotype between breast cancer patients vs healthy; b) Variant genotypes vs wild type genotype between breast cancer patients vs healthy women; c) breast cancer patients with FH; d) breast cancer patients without FH

polymorphisms have been identified in *P53* gene and associated with breast cancer risk. Wang-Gohrke et al.[128] analysed 3 *P53* polymorphisms: *Intron 3 16 bp duplication*, *Arg72Pro* and *Intron 6 MspI G>A*. They showed an increased breast cancer risk in women by the age of 50 years with a first-degree FH only associated to the 16bp duplication polymorphism in intron 3 (OR=5.3 95% CI 1.1-25.6). In a Japanese study[120] was observed an association of breast cancer risk with the *P53 Pro72Pro* genotype (OR=2.14 95% CI 1.21-3.79). Kalemi et al.[129] found higher *P53 Arg72* frequencies in Jewish breast cancer individuals compared with unaffected women. Similar results were obtained in a Turkish population,[130] contrary to the results in the Japanese study already mentioned. Notably, there was no evidence of association between p53 codon 72 polymorphism and breast cancer risk in Tunisian[131] and Russian individuals.[132] In addition, we analysed *P53 16bp Intron3* and *Arg72Pro* polymorphism in 66 breast cancer patients with FH and 197 without FH and 264 healthy women with negative FH. We found higher frequencies of 16bp duplication genotype in breast cancer patients with FH than in the control group (18.4% and 4.7%, respectively) (Table 5). Our results showed a correlation of *16bp Intron3* polymorphism with increased breast cancer risk (OR=4.54 95% CI 1.69 -12.5) in women with a positive FH of breast cancer.

Conclusions

A huge number of studies have tried to elucidate the meaning of DNA signalling and repair polymorphisms to breast cancer susceptibility. However, the results in the literature are controversial and it is very difficult to arrive at a conclusion.

Several reasons and limitations could account for these conflicting results. First, it is known that some polymorphisms frequencies differ greatly from population to population, due to different ethnic characteristics. In this way, future studies should be conducted between homogenous origin groups.

Most of the earlier studies included a small to moderate sample size; and therefore the statistical power of these studies is very limited. The assessment of interactions requires broader studies, especially when rare or very common variants are studied, or else when interactions are moderate.

Many studies included case and control samples with different ages and other features. It is very important that control group share all the characteristics of the case group, except for the disease.

Other sources that may influence results are the differences in the groups concerning specific exposures to a huge variety both of endogenous factors, such as estrogens, immunohistochemistry (e.g. basal and non-basal phenotype) profile and inherited genetic features (*BRCA1* mutations and methylation patters), and exogenous ones, like smoking and dietary habits and occupational exposures. In this way, it is important to consider gene-environment interactions.

DNA signalling and repair pathways assemble numerous genes and they are all interacting to perform the sole purpose of preserving genome integrity. Multiple genes, both within and across pathways, are more likely to be relevant elements of susceptibility than individual polymorphisms. Therefore, it seems critical to evaluate the interaction between the different variants in multiple genes.

The selection of the polymorphism to evaluate is suggested by a high allelic frequency. However, less common variants could also have a functional effect. Therefore, we must consider them. Moreover, a theoretical biological effect of a certain variant is also important in the choice. Nevertheless, functional consequences of most polymorphisms described in these pathways are frequently unknown. Consequently, additional information is needed, including functional *in vitro* and *in vivo* studies correlating genotype and phenotype for variants within breast tissues, and in the diverse situations that mammary cells experience. Furthermore, since the majority of DNA repair proteins interacts with many others proteins, functional studies should evaluate the functional significance of these variants in the context of protein/protein pathways.

Because of the potential relevance to breast carcinogenesis of DNA repair pathways, we conclude that future studies assessing the functional impact of the genetic variation on the DNA repair in breast tissues should be conducted. A rule for genetic variations on breast cancer risk

is suggested by several lines of evidence. Subsequently, these findings need to be replicated in broader studies, with the exam of interactions between variants and relevant carcinogenic risk factors and other genes.

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