Abstract

Breast cancer (BC) is the most common cancer among women worldwide. The aetiology and carcinogenesis of BC are not clearly defined, although genetic, hormonal, lifestyle and environmental risk factors have been established. The most common treatment for BC includes breast-conserving surgery followed by a standard radiotherapy (RT) regimen. However, radiation hypersensitivity and the occurrence of RT-induced toxicity in normal tissue may affect patients’ treatment. The role of DNA repair in cancer has been extensively investigated, and an impaired DNA damage response may increase the risk of BC and individual radiosensitivity. Single nucleotide polymorphisms (SNPs) in DNA repair genes may alter protein function and modulate DNA repair efficiency, influencing the development of various cancers, including breast cancer (BC). SNPs in DNA repair genes have also been studied as predictors for the risk of radiotherapy-induced side effects. We reviewed the literature on the association between SNPs in base excision repair (BER) genes and individual radiosensitivity. We focused on X-ray repair cross complementing group 1 (XRCC1), which plays a key role in BER, and on 8-oxoguanine DNA glycosylase 1, apurinic/apyrimidinic endonuclease 1 and poly (ADP-ribose) polymerase-1, which encode three important BER enzymes that interact with XRCC1. Although no association between SNPs and radiation toxicity has been validated thus far, we also report published studies on XRCC1 SNPs and variants in other BER genes and RT-induced side effects in BC patients, emphasising that large well-designed studies are needed to determine the genetic components of individual radiosensitivity.

Key words: Breast cancer; Polymorphisms; Base excision repair; Susceptibility; Radiosensitivity

Core tip: Single nucleotide polymorphisms (SNPs) in DNA repair genes may modulate DNA repair efficiency, influencing the development of various cancers, including breast cancer (BC). SNPs in DNA repair genes have also been studied as predictors for the risk of radiotherapy-induced side effects. We reviewed the literature on the association between SNPs in base excision repair (BER) genes and individual radiosensitivity. We focused on X-ray repair cross complementing group 1, 8-oxoguanine DNA glycosylase 1, apurinic/apyrimidinic endonuclease 1 and poly (ADP-ribose) polymerase-1, which encode four important BER proteins. We also report published studies on SNPs in BER genes and individual radiosensitivity in BC patients.
INTRODUCTION

Female breast cancer (BC) is the most prevalent malignancy worldwide, with 5.2 million cases diagnosed between 2004 and 2008[1], and it is the primary cause of cancer-related death among women (http://globocan.iarc.fr).

Breast cancer is considered a multifactorial disease, and its occurrence is related to genetic, reproductive, environmental and lifestyle factors.

Breast cancer susceptibility has a complex genetic basis, which has been widely investigated over the past 20 years. Linkage analysis and a candidate gene approach have been used to identify susceptibility loci for BC with high and moderate penetrance. Rare mutations, principally in genes involved in DNA repair such as BRCA1, BRCA2, TP53, ATM, CHEK2, PALB2 and BRIP1, are associated with a greatly increased risk of BC[2].

Case-control and, in recent years, genome-wide association studies (GWAS) have identified more than 70 low-penetrance common variants [single nucleotide polymorphisms (SNPs)] associated with BC risk. Although many of the associations identified in GWAS are localised in non-coding regions of the genome, which are most likely involved in gene expression regulation, some common patterns have been identified among the BC susceptibility loci. Low-penetrance BC loci are related to mammary gland development, the DNA repair pathway, growth factors, the cell cycle, differentiation and apoptosis[3].

Common SNPs in DNA repair genes have been extensively investigated in candidate-gene and case-control association studies in the context of breast carcinoma and other types of cancer. SNPs in such genes can affect the efficiency of the DNA repair machinery and contribute to genomic instability and cancer development[4].

Among the different DNA repair pathways, base excision repair (BER) is responsible for the repair of bases damaged by the effects of X-rays, reactive oxygen radicals and alkylating agents. Many epidemiological studies have investigated the association between common variants in BER genes and human cancer, including breast cancer[5]. Furthermore, DNA repair genes, including BER genes, have been extensively examined in several epidemiological studies to determine their association with radiation-induced toxicity in cancer patients undergoing radiotherapy (RT)[6]. In fact, inter-individual differences in response to therapeutic radiation exposure have been observed, and this variability may be influenced by genetic factors affecting DNA repair efficiency[7]. The side effects induced by RT in normal tissue largely depend on the capacity of cells to repair DNA damage caused by irradiation.

Here, we survey association studies on the most common variants in BER genes, evaluating their role in BC susceptibility and in the risk of developing adverse reactions after RT.

BER PATHWAY

The BER pathway is the primary mechanism that protects cells from oxidative DNA damage; it acts on small DNA lesions or modified bases, where it removes and replaces the damaged base[8]. This process starts with the release of the damaged base by base-specific DNA glycosylases (e.g., the oxidised base 8-oxoguanine is excised by 8-oxoguanine DNA glycosylase), followed by the cleavage of the sugar-phosphate chain, excision of the apurinic/apyrimidinic (AP) site by endonuclease action, DNA synthesis and ligation (Figure 1). This pathway is referred to as short-patch BER and results in the replacement of the AP site via the incorporation of a single nucleotide. In contrast, the long-patch BER pathway produces a repair tract of at least two nucleotides[9]

Enzymes involved in BER include 8-oxoguanine DNA glycosylase 1 (OGG1); AP endonuclease 1 (APE1 or APEX1), which excises the abasic residue; poly (ADP-ribose) polymerase-1 (PARP-1); PARP-1: Poly (ADP-ribose) polymerase-1; XRCC1: X-ray repair cross complementing group 1; Polβ: DNA polymerase-β; LIGⅢ: DNA ligase Ⅲ.

Figure 1  Base-excision repair. Simplified schematic representation of the short-patch base-excision repair pathway showing the key steps and main proteins involved in the repair of a damaged DNA base. Adapted from Costa et al[6]. OGG1: 8-oxoguanine DNA glycosylase 1; APE1: Apurinic/apyrimidinic endonuclease 1; PARP-1: Poly (ADP-ribose) polymerase-1; XRCC1: X-ray repair cross complementing group 1; Polβ: DNA polymerase-β; LIGⅢ: DNA ligase Ⅲ.
of the DNA substrate from the DNA glycosylase product to the AP endonuclease. Polβ is then recruited by its interactions with APE1 and XRCC1. The binding of XRCC1 with PARP-1 also plays a role in BER. Moreover, XRCC1 is essential for the stabilisation of LIGⅢ.

Interactions between XRCC1 and its BER partners are mediated by different domains of the protein, which introduces the possibility that all four proteins, namely XRCC1, Polβ, PARP-1 and LIGⅢ, could form a single complex[11]. Some of the interactions between BER proteins are illustrated in Figure 1.

Many polymorphisms have been identified in genes encoding proteins involved in BER and in other DNA repair pathways[12]. In particular, many epidemiological studies have been performed to evaluate the association between XRCC1 SNPs and different types of cancer[13].

SNPs IN BER GENES AND BREAST CANCER RISK

XRCC1 gene

The human XRCC1 gene maps to chromosome 19q13.2 and encodes a scaffold protein of 633 amino acids that plays a major role in the BER pathway and is also involved in other DNA repair mechanisms, such as single-strand break repair and non-homologous end joining. XRCC1 interacts with several BER proteins such as DNA polymerase β, APE1, OGG1, PARP-1 and LIGⅢ[14]. A schematic representation of XRCC1 and its interactions is shown in Figure 2A.

Among the many SNPs found in the XRCC1 gene, three polymorphisms resulting in non-conservative amino acid substitutions have been identified: Arg194Trp (rs1799782), Arg280His (rs25489) and Arg399Gln (rs25487)[15]. Another XRCC1 variant located in the 5'-untranslated region (5'UTR), -77 T > C (rs3213245), was identified in 2004[16]. The structure of the XRCC1 gene and the localisation of the most common SNPs are illustrated in Figure 2B. XRCC1 variants could affect the function of the protein and impair DNA repair efficiency. In particular, the XRCC1 Arg399Gln variant has been the subject of many case-control studies to investigate its possible association with breast cancer risk. The published data on this association, which are often contradictory, have been collected in several meta-analyses[17-20] (Table 1). Huang et al[17] showed that the Arg399Gln SNP is associated with a trend of increased breast cancer risk using both dominant and recessive models. In ethnic subgroups, and considering the recessive model, this polymorphism is associated with BC risk in Asians and Africans, although it is weakly related with breast cancer in Caucasians. The association between the Arg399Gln variant and BC risk was confirmed in Asian and African populations[18,19], whereas other studies confirmed these data only among Asians[18,20]. These findings suggest that the role of the XRCC1 Arg399Gln SNP as a risk factor for breast cancer may differ between Caucasian and Asian populations.

A very recent meta-analysis of 297 case-control studies evaluated the association between the XRCC1 Arg399Gln polymorphism and overall cancer risk[13], a significantly increased cancer risk was found in all genetic models. In stratified analyses by cancer type, significantly increased cancer risk was found in all genetic models. In ethnic subgroups, and considering the recessive model, this polymorphism is associated with a trend of increased breast cancer risk using both dominant and recessive models. In ethnic subgroups, and considering the recessive model, this polymorphism is associated with BC risk in Asians and Africans, although it is weakly related with breast cancer in Caucasians. The association between the Arg399Gln variant and BC risk was confirmed in Asian and African populations[18,19], whereas other studies confirmed these data only among Asians[18,20]. These findings suggest that the role of the XRCC1 Arg399Gln SNP as a risk factor for breast cancer may differ between Caucasian and Asian populations.

XRCC1 haplotypes

Some case-control studies assessing the association between XRCC1 haplotype and susceptibility to breast cancer were collected in a meta-analysis[21]. Haplotypes for the most common non-synonymous XRCC1 SNPs...
(Arg194Trp and Arg399Gln) were considered, and the analysis showed a slight increased risk of BC associated with the Arg194-Gln399 haplotype in comparison with the Arg194-Arg399 haplotype. In the stratified analysis according to geographic location, the Arg194-Gln399 haplotype was significantly associated with breast cancer risk among individuals from Asian countries, while no association has been found between the XRCC1 haplotype and BC susceptibility in Caucasian populations.

Thus far, a few XRCC1 haplotype analyses have included the -77 T > C SNP in the 5'UTR[10,24]. Two studies[22,24], one performed on French and the other performed on Chinese BC patients and controls, considered XRCC1 SNPs at position -77 and at codons 194, 280 and 399. Brem et al[22] found that the haplotype carrying the variant allele at codon 280 and the wild-type (wt) alleles at the other positions was associated with an increased risk of BC, although the association was not significant. In contrast, Liu et al[24] observed a significantly higher BC risk for the haplotype containing the variant allele at position -77 and the wt alleles at other positions.

In a case-control study on Caucasian BC patients, Sterpone et al[23] performed a haplotype analysis based on XRCC1 genotypes at position -77 and at codons 194 and 399. The haplotype containing the wt allele at position 194 and the variant alleles at other positions was significantly associated with a higher BC risk in this study.

**OGG1 gene**

The human OGG1 gene is located on chromosome 3p26.2 and encodes the key enzyme in the repair of 8-oxoguanine, which is one of the most common products generated by exposure to reactive oxygen species[25]. Among the SNPs in OGG1, the most studied variant is the functional substitution Ser326Cys (rs1052133), which is located in exon 7 of the OGG1 gene and causes an amino acid change (from serine to cysteine). Comparative functional analysis via a complementation assay of a defective *Escherichia coli* mutant revealed that the repair activity of the 326Ser protein was higher than that of the 326Cys protein[26]. Therefore, this OGG1 polymorphism may result in changes in DNA repair activity in human cells.

Many studies that have highlighted the association between the OGG1 Ser326Cys SNP and breast cancer risk have produced conflicting results. To clarify the findings, several meta-analyses have been performed (Table 2)[27-29]. Yuan et al[27] collected data published from 2003 to 2008 and evaluated the association between the OGG1 Ser326Cys SNP and BC onset according to menopausal status and ethnicity by performing a stratified analysis. This meta-analysis suggested that the 326Cys allele had a significant protective effect against BC in European women, both in the additive (326Cys allele vs 326Ser allele) and dominant (Cys/Cys + Cys/Ser vs Ser/Ser) genetic models. No significant association was found between this SNP and menopausal status or other ethnicities. These results were discussed by Ding et al[28], who combined all of the studies on European populations and performed a new meta-analysis, which indicated a lack of association between the OGG1 326Cys allele and BC risk for this ethnicity. This result was confirmed by the meta-analysis performed by Gu et al[29], who identified 11 case-control studies published from 2003 to 2009; however, they did not observe any significant association between Ser326Cys SNP and BC risk, even in the analyses stratified by ethnicity, source of controls and menopausal status. An additional case-control study not included in the aforementioned meta-analysis also showed a lack of association between the OGG1 Ser326Cys variant and BC susceptibility[30].

Nevertheless, a recent study in a Korean population[31] revealed that different SNPs in BER genes (including the OGG1 Ser326Cys and rs2072668 SNPs) function in combination to increase the risk of breast cancer. Another recent study showed that OGG1 Ser326Cys was significantly associated with an increased BC risk in specific subgroups of Chinese Han women (younger than 55 years, premenopausal, triple-negative or p53-positive)[32]. The Ser326Cys SNP was also significantly associated

### Table 1 List of meta-analyses on X-ray repair cross-complementing group 1 single nucleotide polymorphisms and haplotypes and risk of breast cancer

| Ref.          | XRCC1 SNPs         | Number of studies analysed | Result                                                                                     |
|--------------|--------------------|----------------------------|--------------------------------------------------------------------------------------------|
| Huang et al[10] | Arg399Gln, Arg194Trp, Arg280His | 37                         | The 399Gln variant allele is associated with an increased risk of BC                        |
| Li et al[10]  | Arg399Gln, Arg194Trp, Arg280His | 8                          | The recessive effect of the 399Gln variant allele increases the risk of BC (significant only in Asians) |
| Wu et al[26]  | Arg399Gln, Arg194Trp, Arg280His | 44                         | This SNP is associated with increased BC risk in Asians and Africans                        |
| Saadat et al[21] | Arg399Gln, Arg194Trp, Arg280His | 36                         | This SNP is associated with increased BC risk in Asians                                      |
| Yi et al[22]  | Arg399Gln, Arg194Trp, Arg280His | 54                         | This SNP is associated with increased risk of BC in Asians and Indians                       |
| Saadat[33]    | Arg399Gln, Arg194Trp, Arg280His | 10                         | The Arg194-Gln399 haplotype is associated with increased BC risk in Asians                   |

XRCC1: X-ray repair cross-complementing group 1; SNP: Single nucleotide polymorphism; BC: Breast cancer; Arg: Arginine; Gln: Glutamine; His: Histidine; Trp: Tryptophan.
with overall cancer risk in a more recent meta-analysis\(^,[33]\) and it showed a stronger association with lung cancer risk.

Therefore, there is evidence that the **OGG1** Ser326Cys polymorphism is associated with cancer risk, and in particular that it may be a low-penetration susceptibility factor for lung cancer. Moreover, the Ser326Cys variation could interact with other factors such as age, triple-negative status and p53-positive status, thereby influencing breast cancer carcinogenesis.

### **PARP-1 and APE1 genes**

**PARP-1**, also referred to as ADP ribosyl transferase, and **APE1** are two of the most important enzymes in the BER pathway.

The human **PARP-1** gene is localised to chromosome 1q41-42 and encodes a nuclear protein that specifically recognises and binds DNA strand breaks. **PARP-1** also recruits other BER proteins, including the **XRCC1-LIG III** complex, to facilitate the core BER reaction.

**APE1** initiates the restoration step of the BER pathway by hydrolysing the 5'-phosphodiester bond of the AP site\(^,[5]\). The human **APE1** gene maps to chromosome 14q12\(^,[34]\).

Several studies have assessed the association between common polymorphisms (**PARP-1** Val762Ala-rs1136410 and **APE1** Asp148Glu-rs3136820) in these two BER genes and BC risk, although inconclusive results were obtained. A meta-analysis of the literature, updated to 2011, was performed to obtain a more accurate estimate of this association\(^,[35]\). In total, 8 studies were included in the meta-analysis (Table 2). No association between **PARP-1** Val762Ala and breast cancer risk was found in any of the genetic models. Additionally, there was no association between BC risk and **APE1** Asp148Glu considering all genetic models; therefore, the analysis suggests that these two polymorphisms are not associated with BC susceptibility.

Two additional papers on **APE1** SNPs and breast cancer risk were recently published\(^,[36,31]\). A case-control study performed on a Chinese population reported no association between Asp148Glu and BC susceptibility, as indicated by the above-cited meta-analysis. In contrast, a significant association between a SNP in the **APE1** promoter (-65 T > G) and decreased BC risk was found, suggesting that this polymorphism may influence breast cancer occurrence\(^,[31]\). In a study by Kim et al\(^,[31]\), the association between **APE1** Asp148Glu and two **OGG1** SNPs, including **OGG1** Ser326Cys, and BC risk was evaluated. Whereas **APE1** Asp148Glu was weakly associated with BC risk, a combined analysis including the two BER genes revealed a significant effect on breast cancer occurrence, suggesting the importance of assessing a combination of SNPs in different genes and gene haplotypes for the prediction of BC risk.

### **SNPs IN BER GENES AND RADIosenSITIVITY**

Breast-conserving surgery followed by a standard RT regimen is the most common treatment for breast cancer. However, therapeutic exposure to IR can induce adverse reactions in normal tissue. These reactions show considerable variation among individuals, suggesting the involvement of genetic factors. Because IR hypersensitivity may lead to interruption of therapy, in the last several years, significant effort has been devoted to the identification of molecular factors that could increase radiotherapy-induced side effects.

SNPs in genes involved in processes such as DNA repair, cell-cycle control, apoptosis, cellular antioxidant defence and cytokine production may influence the individual radioresponse. Several experimental approaches, such as candidate SNP association studies and GWAS, are being used to investigate the genetic basis of normal tissue radiosensitivity\(^,[37]\). Radiogenomics studies are most numerous in breast cancer patients treated with RT and are aimed at identifying SNP profiles that can be used to select radiosensitive patients. In particular, several studies on BC patients evaluating the association between the risk of acute and late skin reactions to RT and SNPs in DNA repair genes (especially **XRCC1**) were performed; however, these studies yielded conflicting results. Eleven studies on **XRCC1** SNPs, mainly involving Caucasian patients, were collected in a recent meta-analysis\(^,[38]\).
No predictive value was found for this SNP

Result
The 280His variant allele is protective against RT-induced toxicity (in BC patients treated with RT only)

Table 3  Association between X-ray repair cross-complementing group 1 single nucleotide polymorphisms and radiotherapy-induced side effects in breast cancer patients

| Ref. | XRCC1 SNPs | Number of studies analysed | Result |
|------|------------|---------------------------|--------|
| Xie et al[45] | Arg399Gln | 8 | The 399Gln variant allele is associated with a higher risk of RT-induced toxicity (only in some subgroups of BC patients) |
| | Arg194Trp | 6 | No predictive value was found for this SNP |
| | -77 T > C | 4 | No predictive value was found for this SNP |
| | Arg280His | 4 | The 280His variant allele is protective against RT-induced toxicity (in BC patients treated with RT only) |

XRCC1: X-ray repair cross-complementing group 1; SNP: Single nucleotide polymorphism; RT: Radiotherapy; BC: Breast cancer; Arg: Arginine; Gln: Glutamine; Trp: Tryptophan; His: Histidine; T: Thymine; C: Cytosine.

In these studies, the severity of acute and/or late side effects of RT was assessed according to various evaluation criteria, including the Common Terminology Criteria for Adverse Events (CTCAE) [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcaev3.pdf], the criteria proposed by the Radiation Therapy Oncology Group (RTOG) and European Organization for Research and Treatment of Cancer (EORTC) [39], the Late Effects of Normal Tissue-Subjective Objective Management Analytical (LENT/SOMA) [40] and the Common Toxicity Criteria of the United States National Institutes of Health (NIH) [http://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/ctcmanual_v4_10-4-99.pdf#search="ctc"]).

To evaluate acute RT side effects in BC patients, the following clinical skin reactions within the radiation field of the breast were documented during treatment: erythema, epilation, desquamation and decreased sweating in addition to more severe morbidities such as edema, ulceration, haemorrhage and necrosis. Common late radiation effects (i.e., effects that first occur at least 90 days after the initiation of RT) include fibrosis, telangiectasia and atrophy.

Both early and late normal tissue reactions are graded on a 5-point ordinal scale (0 indicating absence of a radiation effect and 5 indicating an effect leading to death). The grade of toxicity induced by radiotherapy was assessed according to different evaluation criteria, with high-grade toxicity considered as grade ≥ 2 (according to CTCAE, RTOG-EORTC and LENT/SOMA) or grade ≥ 2e (according to the NIH).

The results of the meta-analysis by Xie et al[38] are summarised in Table 3. No significant association between the XRCC1 Arg399Gln SNP and IR-induced toxicity was observed in the overall analysis. Nevertheless, stratified analyses showed that the Arg399Gln SNP was predictive of side effects in some subgroups of BC patients. For example, carriers of the XRCC1 399Gln allele were at higher risk of RT-induced side effects in studies using high-quality genotyping methods, in studies with mixed treatment regimens or when studies on only late toxicity were excluded. On the contrary, the XRCC1 Arg280His variant allele had a protective effect against RT-induced toxicity only in BC patients treated with radiotherapy alone. XRCC1 Arg194Trp and -77 T > C did not have any predictive value.

This analysis indicated that large well-designed studies are needed to more clearly establish the predictive value of XRCC1 variants and SNPs in other DNA repair genes for radiation-induced side effects. The choice of genotyping method and the selection of well-characterised patient cohorts should be carefully considered.

Few studies investigating the association between SNPs in other BER genes and the risk of adverse reactions to RT in BC patients are available in the literature. Concerning the APE1 Asp148Glu SNP, the 148Glu allele was found to have a protective effect against the development of acute toxicity to radiation in Caucasian BC patients; however, this effect was only observed in the normal-weight subgroup of patients [41]. Moreover, the authors observed that the APE1 148Glu and XRCC1 399Gln alleles exerted a combined protective effect. No association between APE1 SNPs and late complications in normal tissue after radiotherapy has been identified thus far for BC [42,43].

The association of DNA repair SNPs with late RT effects in normal tissue has also been investigated in prostate cancer patients, although the radiogenomics studies reported thus far present interpretive difficulties because of numerous confounding factors [37]. A GWAS was recently performed to identify SNPs associated with the development of erectile dysfunction following RT for prostate cancer [44]. Twelve candidate SNPs identified in this study were associated with cellular functions such as adhesion, signalling and hormone metabolism rather than DNA damage repair. Therefore, the involvement of DNA repair SNPs in the radiosresponse after RT for prostate cancer remains an open question.

Few studies have examined patient populations with tumours other than carcinomas of the breast or prostate, although significant acute and late toxicities are frequent in patients with squamous carcinomas of the head and neck who are treated with RT. The association of DNA repair SNPs with effects on normal tissue in the head and neck and in other types of cancers should be more extensively explored [37].

The attempts made thus far to validate the published data on genotype and radiation toxicity did not confirm a clinically relevant predictive value for any published SNP [46]. Currently, it remains controversial whether SNPs could significantly influence the risk of complications in normal tissue [46].
CONCLUSION

In the last decade, there has been increasing interest in identifying associations between SNPs in DNA repair genes and susceptibility to various cancers, including BC\(^1,2\). In this context, BER gene polymorphisms have been extensively investigated; however, their association with BC has not been clearly defined. The Arg399Gln SNP, which is the most common variant in the XRCC1 gene, showed an overall weak association with BC risk that became stronger only for some ethnicities. In general, SNPs may contribute to the genetic risk for BC, although their effect is usually only slightly statistically significant. In some studies, SNP-SNP interactions have been examined to evaluate epistatic effects contributing to BC\(^3,4\). SNPs in different DNA repair pathways, or in other pathways related to DNA metabolism, were selected, and specific SNP pairs showed a statistical association with BC risk. Significant trends in BC risk were also observed in association with an increasing number of risk alleles in different DNA repair genes\(^5,6\). Concerning BER genes, XRCC1 SNPs and haplotypes play an important role because they result in amino acid substitutions, which may affect the interaction of the protein with the other BER enzymes and alter DNA repair efficiency. Studies on the interaction between SNPs in BER genes should be encouraged because although a single SNP may have a negligible effect, interactions between different SNPs in genes of the BER pathway could significantly affect cancer risk.

Studies on the interactions between SNPs in genes of different DNA damage signalling and repair pathways should also be performed. Newly available techniques, principally GWAS, will help to explain the role of moderate-risk alleles and common lower-penetrance alleles in sporadic and familial BC risk.

Furthermore, gene-environment interactions should be investigated to elucidate the complex mechanism underlying BC carcinogenesis. Similarly, it has been demonstrated that SNPs in BER genes (particularly APE1 and XRCC1) may contribute to IR hypersensitivity. Until now, no association between SNPs and late toxicity has been confirmed, either for BC or for prostate cancer\(^7\). Therefore, large, well-designed studies are needed to obtain more robust results.

Although the analysis of gene polymorphisms for the individualisation of cancer therapy is not yet widespread in routine clinical practice, understanding the genetic components of individual radiosensitivity remains an important goal. To properly assess the value of pre-treatment genotyping approaches, prospective collection of genomic DNA from patients enrolled in clinical trials should be planned to develop personalised radiotherapy protocols for both sensitive and resistant patients.

The establishment of gene polymorphism databases will significantly contribute to these tasks, and meta-analyses that collect a large amount of data will permit faster access to scientific results.

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