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DNA Repair Perspectives in Thyroid and Breast Cancer: The Role of DNA Repair Polymorphisms

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1. Introduction

One of the great challenges of modern molecular biology is the integration of new genetic information into procedures that can be implemented in rapid, cost effective and reliable methods to genotype, phenotype, identify gene function, and development treatment for the disease. One of the major impacts of such methods and procedures is the increase of our knowledge and understanding of human biology leading to the recognition of the importance of molecular factors in disease aetiology. The immediate consequence of such knowledge is an increased ability for pathology diagnostic and for the identification of pre-symptomatic individuals or those susceptible to specific diseases, improving our ability for disease prognosis and to develop more efficient therapeutic strategies.

Every organism is exposed to hazardous agents in its environment on a continual basis. As a result, organisms have evolved sophisticated pathways that are considered an environmental response machinery, to minimize the biological consequences of hazardous environmental agents. A large number of human genes, including the ones involved in the environmental response machinery, are subject to genetic variability, which can be associated with the altered efficiency of a biological pathway (Perera & Weinstein, 2000). So, an individual's risk for developing a disease stemming from an environmental exposure might be dependent on the efficiency of his/her own unique set of environmental response genes. These genes are usually involved in the metabolism of environmental carcinogens, in the repair of DNA lesions induced by exogenous and endogenous carcinogens, and in the control of the cell cycle. Individual polymorphic forms in those genes have been associated with individual susceptibility to different types of cancer namely in breast and thyroid cancer (Conde et al., 2009; Gaspar et al., 2004; Pabalan et al., 2010; Peng et al., 2011; Silva et al., 2005; Silva et al., 2006b; Silva et al., 2006a; Silva et al., 2009; Silva et al., 2010; Silva et al., 2007).

Several enzymes have evolved for the detoxification of xenobiotic compounds, and their gene expression is induced in response to the presence of numerous compounds *(e.g.,* polycyclic aromatic hydrocarbons found in tobacco smoke). An inefficient detoxification of reactive endogenous or exogenous compounds ultimately leads to lesions in DNA, which should be repaired by DNA repair mechanisms, ought to reduce cancer risk. As a

consequence, a genetic change that alters the expression of the gene or the activity of the detoxifying protein produced may increase the amount of reactive carcinogen present, thus, increasing the risk of cancer development. As an example, CYP1A1 and CYP2D6 phase I enzymes, are induced by, and act on, carcinogens found in tobacco smoke. Additionally, CYP2E1, an enzyme that metabolizes ethanol, is also a candidate because epidemiological studies suggest that breast cancer risk is increased with alcohol consumption (Hasler, 1999).

Environmental carcinogens interact with DNA as a result of complex metabolisms, involving phase I and phase II enzymes giving rise to several biomarkers of lesion. There are several specific biomarkers for evaluation of specific exposures. For instance, several environmental carcinogenic compounds (e.g. Aflatoxin B1, Benzo(a)Pyrene) react with DNA and/or proteins giving rise to specific adducts (Taioli et al., 2007; Wu et al., 2002). However, apart from the specific biomarkers, exposure to these compounds leads to appearance of unspecific biomarkers as well (El-Zein et al., 2011).

In spite of being usually unspecific biomarkers of lesion, there is evidence of correlation between increased frequency of chromosomal aberration (CA), micronuclei and cancer incidence in humans, which supports the use of cytogenetic human monitoring for cancer risk assessment (Bonassi et al., 2007; Bonassi et al., 2011; Dhillon et al., 2011). The levels of the different biomarkers studied are not directly correlated with the levels of exposure, suggesting that intra-individual susceptibility plays an important role. Several studies have shown that the level of biomarkers arising from environmental and/or occupational exposure may be modulated by polymorphic genes (Bonassi et al., 2011; Dhillon et al., 2011; Pavanello & Clonfero, 2000). As an example, experiments conducted in our laboratory concerning the evaluation of occupational exposure to Polycyclic Aromatic Hydrocarbons (PAHs), showed that the levels of aromatic DNA adducts are higher in smokers than in non smokers and the individual levels of DNA adducts in smokers is dependent on the *CYP1A1 Msp*I polymorphism, located in the 3´ non-coding region of the gene, and that the presence of at least one allele with the restriction site leads to a significant higher level of DNA adducts when compared with the ones homozygous for the absence of this restriction site (Teixeira et al., 2002). Interestingly the same *CYP1A1* polymorphism has been associated with lung cancer risk among the Japanese and Caucasian populations (Kawajiri et al., 1990; Xu et al., 1996). The dependence of biomarkers' level with individual genotypes is also observed in human tumours. For instance, in lung cancer patients the level of DNA adducts has been correlated with *CYP1A1* activity (Mollerup et al., 1999), and also with the *GSTP* polymorphisms (Rydberg et al., 1996). Thus, the parallel study of polymorphic genes associated with cancer susceptibility, and their correlation with biomarkers of exposure to carcinogens will improve our knowledge on the correlation between environmental exposure and individual variability. Additionally, these results prove the relevance of DNA repair pathways in cancer susceptibility, working as one important tool when other mechanisms fail.

The data concerning the individual levels of biomarkers of exposure and the association between individual genetic polymorphisms and cancer risk suggest the involvement of environmental factors in some human cancers (e.g. carcinogen exposure) with individual risk factors (e.g. genetic polymorphisms). Thus, the parallel study of polymorphic genes associated with cancer susceptibility, and their correlation with biomarkers of exposure will improve our knowledge on the correlation between environmental exposure and individual variability (Rueff et al., 2002) to different types of cancer namely in breast and thyroid cancers.

1.1 Breast cancer

Breast cancer is the most common form of cancer among women, being responsible for the highest mortality rate from cancer among the female sex. However, the main causes related to this pathology remain unclear. The risk of neoplasic disease has been connected with genetic and environmental factors. In fact, genes and the environment share the stage for most, if not all, common non-familial cancers, and are related to individual susceptibility.

Several studies have identified two major susceptibility genes in breast cancer: *BRCA1* and *BRCA2* (Hedenfalk et al., 2003; Narod & Foulkes, 2004). These genes have an important role in genome maintenance, in cell cycle control and in DNA repair, controlling homologous recombination repair (Scully & Puget, 2002; Venkitaraman, 2002). Analysis in families with high risk of breast cancer showed that individuals with point mutations in these genes have a 40-80% of probability to develop breast cancer. However, mutations in these two tumour-suppressor genes account for only 5-10% of all cases of breast cancer (Fackenthal & Olopade, 2007).

Factors related to reproductive history and/or hormonal status have been found to confer increased risk (e.g., nulliparity, late age at first pregnancy, early menarche, late menopause), but the magnitude of the increased risk is generally not huge (less than 3) and the majority of breast cancer cases occur in women not demonstrably at high risk for this tumour. Recent evidence shows that there are other background genetic factors that contribute to the development of breast cancer, such as polymorphisms in DNA repair pathways that might increase cancer risk (Hunter et al., 2005; Silva et al., 2007).

1.2 Thyroid cancer

Thyroid cancer is the most frequent endocrine neoplasia, accounting for 1-5% of all cancers in women and 2% in men in most countries, being responsible for 0.32% of deaths related to malignant tumours. The incidence of this type of tumour has been responsible for 6.3% of total deaths promoted by endocrine tumours, which reflects its indolent nature. Nevertheless, 5-10% of all thyroid cancers are fatal (Inskip, 2001).

The high frequency of cancer among family members of thyroid cancer patients supports the hypothesis that hereditary factors are important in the aetiology of this tumour. Among the sporadic cases of thyroid cancer the most common histological varieties are non-familial papillary and follicular thyroid carcinomas which shows a long-term (~10-year) survival rate of more than 90%. These diseases are unusual in children and adolescents, and their incidence increases with age in adults, with the majority of cases occurring between 25 and 65 years of age. The papillary and follicular carcinomas are two to four times more frequent in women than in men, particularly during reproductive years, leading to the hypothesis that female hormones may be involved in the aetiology or pathogenesis of the disease (Grubbs et al., 2008). Exposure to ionizing radiation is the only verified cause of thyroid carcinogenesis in humans, especially when exposure occurs at a young age. However, individuals without previous exposure to ionizing radiation can also develop thyroid cancers, suggesting that other risk factors may also be involved in the aetiology of sporadic tumours. For example, dietary iodine deficiency has also been linked to this pathology. In fact, papillary tumours associated with radiation exposure usually have different forms of the activated *RET* proto-oncogene and at a higher frequency than that observed in spontaneous non-radiation induced tumours (Grubbs et

al., 2008; Sarasin et al., 1999), while follicular tumours are associated with somatic *RAS* gene mutations (Grubbs et al., 2008). Accordingly, the evidences suggested the existence of other risk factors for papillary and follicular tumours. Thus, the identification of susceptibility factors, both genetic and environmental, associated with individual predisposition to thyroid cancer could possibly give further insight into the aetiology of this malignancy.

2. DNA repair pathways

It is generally agreed that genetic polymorphisms are associated with, or are even the cause, of most common disorders with a genetic component like cancer. However, the complex metabolism of xenobiotic compounds involving different polymorphic genes could modulate the individual risk factor for cancer (Pavanello & Clonfero, 2000).

DNA repair enzymes continuously monitor chromosomes to correct damaged nucleotide residues generated by exposure to carcinogens and cytotoxic compounds. The damage is partly a consequence of environmental agents such as ultraviolet (UV) light from the sun, inhaled cigarette smoke or deficient dietary habits. However, a large proportion of DNA alterations are caused unavoidably by endogenous mutagens, such as reactive oxygen species and metabolites that can act as alkylating agents. Genome instability caused by the great variety of DNA-damaging agents would be an overwhelming problem for cells and organisms. Thus, DNA repair is a ubiquitous process throughout the living world and defective DNA repair is a risk factor for many types of cancer. Its universality reflects the constant challenge to the integrity of any genome from the inherent instability of DNA, the natural limitations of the accuracy of DNA synthesis and the challenge of the environment.

Recent evidence that some DNA repair functions are haploinsufficient adds weight to the notion that variants in DNA-repair genes constitute part of the spectrum of defects contributing to cancer risk. A coherent understanding of the genomics of human DNA repair genes, especially single nucleotide polymorphisms (SNPs), will greatly facilitate the investigation of the role that these variations play in modulating carcinogenesis.

Several studies have shown that genes directly involved in DNA repair and in the maintenance of genome integrity, or genes indirectly involved in the repair of DNA damage through the regulation of the cell cycle, are critical for protecting against the mutations that lead to cancer (Hakem, 2008). Evidence suggests that the difference in DNA repair capacity among individuals is genetically determined, and that reduced DNA repair capacity constitutes a statistically significant risk factor for development of several cancers, associated with reduced protein function rather than absence of its function. Recently a number of polymorphisms of genes that encode for DNA repair proteins have been described (Wood et al., 2005). However, we will not discuss the mechanisms of these pathways in detail; instead we will focus on how epidemiologic studies contribute to understand the role of genetic polymorphisms present in DNA repair genes and individual susceptibility to breast and thyroid cancers.

2.1 BER – Base excision repair

The base excision repair (BER) pathway is mainly responsible for the lesion-specific removal that arises from endogenous or exogenous agents inducing base damage, which are the most frequent insult in cellular DNA. Reactive oxygen species (ROS) are produced from

endogenous sources, most notably the oxidative metabolism in the mitochondria, and from exogenous sources, such as ionizing radiation. ROS attack DNA readily, generating a variety of DNA lesions, such as strand breaks and oxidized bases. If not properly removed, DNA damage can be potentially devastating to normal cell physiology, leading to mutagenesis and/or cell death, especially in the case of cytotoxic lesions that block the progression of DNA/RNA polymerases (Maynard et al., 2009). BER pathway involves two sub-pathways, the short-patch responsible for the replacement of a single base, and the long-patch, which results in the incorporation of 2-13 nucleotides. The two pathways progress through different major processes that initially involve the removal of the damage base by glycosylases (Li et al., 2010).

2.1.1 BER and breast cancer

Several enzymes of the BER pathway act in concert to keep the DNA intact and maintain genomic integrity. One of the most studied genes of BER pathway has been the *XRCC1* gene. XRCC1 is a scaffolding protein that is involved in the repair of single-strand breaks, the most common lesion in cellular DNA (Li et al., 2009). Concerning the *XRCC1* gene polymorphisms, several studies suggest a dual effect of these SNPs in cancer risk. In fact, genetic variation in six BER pathway genes (*XRCC1, ADPRT, APEX1, OGG1, LIG3*, and *MUTYH*) is associated with breast cancer risk in two large population-based case-control studies in the United States and Poland (Zhang et al., 2006). Additionally, *XRCC1* haplotypes revealed no significant association between Trp194-Arg399 haplotype and risk of breast cancer, neither in Western nor Asian countries, but a recent meta-analysis has indicated that the Arg194-Gln399 haplotype of *XRCC1* might be a risk factor for breast cancer in Asian countries (Saadat, 2010). However, other meta-analysis suggests that polymorphisms Arg280His and Arg399Gln may modify breast cancer risk differently in Caucasian and Asian populations (Li et al., 2009), and a meta-analysis study between the breast cancer and the *XRCC1* polymorphisms Arg194Trp, Arg399Gln and Arg280His in different inheritance models suggested that Arg399Gln was associated with a trend of increased breast cancer risk when using both dominant and recessive models to analyze the data (Huang et al., 2009).

Results published by our group concerning the breast cancer risk and *XRCC1* Arg194Trp and Arg399Gln polymorphisms do not show any association between these polymorphisms and breast cancer risk, but it was observed that menopausal age together with *XRCC1* Arg194Trp and Arg399Gln polymorphisms might be involved in individual susceptibility towards breast cancer (Silva et al., 2007)

DNA polymerase beta (Polβ) provides most of the gap-filling synthesis at abasic sites of damaged DNA in the base excision repair pathway, a polymorphic key gene in BER. A case-control study has shown two polymorphisms in the Polβ protein, the Pro242Arg and Lys289Met, associated with breast cancer risk and cancer progression. In fact, a strong association between breast cancer occurrence and the TT genotype of the Lys289Met (C to G transition) polymorphism and the CG genotype of the Pro242Arg polymorphism was found. Polymorphism-polymorphism interaction between the TT genotype of the Lys289Met and the CG genotype of the Pro242Arg (C to G transition) polymorphisms increased the risk of breast cancer (Sliwinski et al., 2007)

Several DNA BER repair gene polymorphisms have been described, which affect DNA repair capacity and modulate cancer susceptibility, namely with the risk of acute skin

reactions following radiotherapy. In fact, it was reported that *XRCC1* 399Gln or *APEX1* 148Glu alleles may be protective against acute skin reactions following radiotherapy (Chang-Claude et al., 2005). However, it was not confirmed in breast cancer patients (Bartsch et al., 2007). In addition, in a retrospectively evaluation of SNPs in DNA repair genes, it was observed that *XRCC1* Arg399Gln may be predictive of survival outcome in patients with metastasis breast cancer treated with DNA damaging chemotherapy (Bewick et al., 2006). Outcome and survival in anthracycline-based and cyclophosphamide/ methotrexate/5-fluorouracil-based chemotherapy of invasive breast cancer are unpredictable. It was observed that, carriers of the *XRCC1* 1196 AA genotype had a reduced risk for recurrence/death and patients treated with chemotherapy but not radiotherapy, suggesting that DNA repair enzyme XRCC1 is a potential treatment predictor for the outcome and survival of anthracycline and cyclophosphamide/methotrexate/5-fluorouracil-based chemotherapy of invasive breast cancer (Jaremko et al., 2007). However, among incoherent results, recent studies strongly suggest a main role of BER in chemotherapy (Bewick et al., 2006; Goode et al., 2002b; Kelley & Fishel, 2008) in breast cancer.

2.1.2 BER and thyroid cancer

The results obtained by our group, do not reveal a significant involvement of *XRCC1* Arg194Trp and Arg399Gln, *OGG1* Ser326Cys, *APEX1* Asp148Glu, *MUTYH* Gln335His and *PARP1* Val762Ala polymorphisms on the individual susceptibility towards thyroid cancer, since the frequency of the different genotypes are similar in control and cancer patients population (data not published).

Additionally, since thyroid cancer incidence is recurrently reported to be higher in women (which was also the predominant gender in our case group), we compared genotypic frequencies according to sex among thyroid cancer patients (in order to examine for any sex-specific genetic effect), but the frequency of the different genotypes considered did not differ significantly with gender in thyroid cancer patients (data not published).

Concerning the role of *XRCC1* polymorphisms in thyroid cancer, a study reported by (Ho et al., 2009) showed, in white non-Hispanics, that *XRCC1* 194Trp variant allele may be associated with increased risk of differential thyroid carcinoma (DTC), while the *XRCC1* 399Gln variant allele may be associated with decreased risk of DTC. These results are in agreement with the data reported by (Chiang et al., 2008) in Chinese DTC populations. However, Sigurdson and colleagues (Sigurdson et al., 2009) reported that, among residents near Semipalatinsk, Kazakhstan *XRCC1* Arg194Trp is associated with decreased thyroid nodule risks for increasing minor alleles, and a similar patterns of association were observed for a small number of papillary thyroid cancers. The results in our study do not reveal an association between *XRCC1* Arg194Trp genotypes and thyroid cancer risk, and these differences might be due a different risk factors for thyroid tumours (exposure to ionizing radiation (Sigurdson et al., 2009) *versus* sporadic tumours), and genetic background of different populations.

Concerning *XRCC1* Arg280His polymorphism only a positive association was described in Caucasian populations (Garcia-Quispes et al., 2011). Interestingly, in white non-Hispanics, the *XRCC1* 399Gln variant allele may be associated with decreased risk of DTC, and in Caucasians, who lived in the areas of the Russian Federation and Belarus contaminated with radionuclides from Chernobyl fallout, it was observed that the *XRCC1* Arg399Gln

polymorphism, regardless of radiation exposure, was associated with a decreased risk of Papillary Thyroid Carcinoma (PTC) according to the multiplicative and dominant models of inheritance (Sigurdson et al., 2009). However, we cannot exclude that other *XRCC1* gene polymorphisms may interact, alone or when combined, with other genes such as the ADPRT (Chiang et al., 2008). However, our results do not support an association between thyroid cancer risk and the *XRCC1* Arg399Gln polymorphism, suggesting the need of larger studies and/or a meta-analysis, in order to understand the role of the *XRCC1* polymorphisms in thyroid cancer. Additionally, we can rule out the utility of *XRCC1* haplotypes in predicting DTC risk.

In general, the results reviewed suggest that larger studies are required to define the role of *XRCC1* polymorphisms in susceptibility to well differentiated thyroid cancer. However, the scarcity of data concerning other BER genes creates a gap in knowledge about the effective role of polymorphisms in BER pathway and individual susceptibility to thyroid cancer.

2.2 NER – Nucleotide excision repair

Several DNA repair pathways have evolved to repair DNA adducts and function to prevent genomic instability and promote cell survival. The nucleotide excision repair (NER) pathway is important for DNA repair, removing adducts responsible for the distortion of double helix. Such adducts can be caused by UV irradiation and environmental agents such as tobacco smoke (polycyclic aromatic hydrocarbons). This pathway is also the main mechanism for the repair of bulky DNA adducts generated by breast cancer chemotherapeutic agents, such as platinum drugs and cyclophosphamide and may be involved in the repair of nonbulky DNA lesions that result from oxidative damage (Bewick et al., 2011; Oksenych & Coin, 2010). Failure to eliminate these lesions can lead to oncogenesis, developmental abnormalities and accelerated ageing.

NER pathway involves several proteins that act in order to restore the normal homeostasis of the cell. There are two sub-pathways of the NER pathway, global-genomic-NER (GG-NER) and transcription-coupled NER (TC-NER), which differ only in the step involving recognition of the DNA lesion (Shuck et al., 2008). The complex XPC-HR23B or CSA and CSB proteins are responsible for the initial step in the GG-NER and in TC-NER, respectively. The recognition of the distortion of double helix is followed by the opening of the DNA by the XPB and XPD ATPases/helicases of the transcription/repair factor (TFIIH). TFIIH is a multisubunit factor composed of 10 subunits which catalyses helix opening during NER (Li et al., 2010). The DNA strand opening favors the recruitment of XPA and RPA, which help to enlarge the opened structure and drive the dissociation of the CDK activating kinase (CAK) complex from TFIIH. The recruitment of the endonucleases XPG and XPF triggers dual incision and excision of the protein-free damaged oligonucleotide. The gap is filled by the resynthesis machinery and the DNA extremities sealed (Oksenych & Coin, 2010).

Deficiency in NER results in three rare genetic disorders: *Xeroderma pigmentosum* (XP), trichothiodystrophy (TTD) and Cockayne syndrome (CS), characterize by increased cancer frequencies, neurodegeneration and ageing.

2.2.1 Nucleotide excision repair and breast cancer

Genomic instability is a hallmark of all cancers (Hanahan & Weinberg, 2000). At the cellular level, damaged DNA that is not properly repaired can lead to genomic instability, apoptosis, or senescence, which can greatly affect the organism's development and ageing process

(Hakem, 2008). DNA repair pathways are among the mechanisms most frequently deregulated in cancer. These mechanisms allow non-transformed cells to repair their DNA after specific damage or in some circumstance, to induce apoptosis if repair is not possible. This mechanism protects against uncontrolled proliferation in the context of abnormal genetic background. Disruption of these pathways in cancer produces an increase in chromosome breaks and mutagenesis (Amir et al., 2010).

Several polymorphisms in NER genes have been described. However, studies investigating the association of NER genes polymorphisms with breast cancer risk produced controversial results.

Genetic polymorphisms identified in genes encoding DNA repair enzymes are believed to be candidates for associations with several types of cancers, including breast cancer. One of the most studied NER genes is *ERCC2 (XPD)*, which plays a key role in NER pathway. Several polymorphisms in the *ERCC2* gene have been described, including the commonly occurring Asp312Asn and Lys751Gln. However, the published results have been contradictory. Recently, one meta-analysis study revealed no association between both polymorphisms and breast cancer risk (Pabalan et al., 2010). We had also reported similar results previously (Silva et al., 2006a). The main causes for breast cancer remain unclear; however some environmental compounds have been regarded as increasing the risk of breast cancer, especially the ones responsible for generation of DNA adducts (PAHs, aromatic amines). The *ERCC2* polymorphisms have been extensively correlated with high levels of DNA adducts (or lower DNA repair capacity). This reduction in DNA repair capacity is also influenced by these polymorphic variations, being predictive of DNA repair capacity (Crew et al., 2007; Shi et al., 2004).

Other genes of NER pathway have been studied, though not so often, in association studies. For example, the gene *ERCC4 (XPF)* that codes for the subunit of the protein complex ERCC1-ERCC4 responsible for the removal of the damaged single-stranded fragment (Lee et al., 2005), have been studied and the results revealed a significant association of Arg415Gln polymorphism and breast cancer risk (Smith et al., 2003), but not for Ser835Ser polymorphism as described by Lee and colleagues. This research team showed a combined effect between the *ERCC4* synonymous polymorphism and Asp312Asn *ERCC2* polymorphism (Lee et al., 2005). The other sub-unit of protein complex ERCC1-ERCC4, coded by *ERCC1* gene, has also been a target of some epidemiologic studies (Bewick et al., 2011; Crew et al., 2007; Lee et al., 2005; Shin et al., 2008), resulting in contradictory data.

XPG (*ERCC5*) gene is also required for the removal of the damaged single-stranded nucleotide fragment, together with the complex ERCC1-ERCC4. Rajaraman and colleagues described in their work the relevance of one polymorphism of *ERCC5* gene providing suggestive evidence that variant allele of Asp1104His was associated with increased risk of breast cancer overall, and suggesting further an increased susceptibility to breast cancer in radiologic technologists exposed to low levels of radiation (Rajaraman et al., 2008). However, there is no agreement regarding the role of this gene in breast cancer susceptibility (Crew et al., 2007; Jorgensen et al., 2007; Kumar et al., 2003; Mechanic et al., 2006; Shen et al., 2006).

XPC encodes a basic protein that is essential for damage recognition in sub-pathway GG-NER (Sugasawa, 2008). Several studies have been developed concerning the role of *XPC* gene polymorphisms in breast cancer risk. However, the results have been inconsistent. Early this year a meta-analysis including 11 studies was published revealing no associations between the polymorphisms of *XPC* gene under study and breast cancer risk (Zheng et al., 2011). However, the role of this gene in breast cancer should not be excluded, since it was

shown that *XPC* gene, as other *XP* gene products, interact with and stimulate specific DNA glycosylases (e.g. thymine DNA glycosylase (TDG)), initiators of BER, beyond their functions in NER pathway (Sugasawa, 2008). Moreover, gene–gene and gene–environment interactions should also be considered which are not in the meta-analysis studies.

XPA protein interacts with many of the core repair factors in NER pathway, and without it, no stable pre-incision complex can form, nor can NER occur, making it the limiting factor in damage recognition (Shuck et al., 2008). However, *XPA* gene has not been extensively studied in connection with breast cancer risk (Crew et al., 2007; Jelonek et al., 2010; Shen et al., 2006), and the results published did not described this gene as potentially related with breast cancer risk.

Many more polymorphisms in the NER genes have been found, however there aren't enough consistent epidemiologic studies into the link between this pathway and breast cancer. More studies are needed to form any reliable conclusions.

The new era in cancer treatment and prevention lies in the ability to treat patients individually according to their genetic constitution and the DNA repair status of their tumours. The nature of DNA lesions caused by therapeutic agents requires complex repair mechanisms, possibly involving simultaneously different repair pathways. DNA damage acquired from these treatments can initiate a number of cellular pathways involved in DNA repair, cell cycle control, metabolism and apoptosis (Bewick et al., 2011). For example, it is well known the importance of NER pathway in repair of bulky DNA adducts, such those caused by tobacco smoke as well as intrastrand cross-links (ICL) caused by chemotherapeutic agents, such as *cis*-platinum or anthracyclines (Latimer et al., 2010; Saffi et al., 2010). If so, SNPs in genes in this pathway may significantly affect DNA repair efficiency, influencing clinical outcome and thus may help identify patients that can benefit from certain treatments.

2.2.2 Nucleotide excision repair and thyroid cancer

The main, and well documented, cause for thyroid cancer is ionizing radiation, although other risk factors have been pointed out as candidates, such as dietary iodine deficiency, hormonal factors, lymphocytic thyroiditis and familial history (Kondo et al., 2006).

In a previous report, we found a significant association between a haplotype of two SNPs (Asp312Asn and Lys751Gln) in *ERCC2* gene, and thyroid cancer risk (Silva et al., 2005) suggesting that this pathway may be relevant for thyroid carcinogenesis. Later we also conducted another study including more SNPs in different genes of NER (*CCNH* Val270Ala, *CDK7* Asn33Asn, *RAD23B* Ala249Val, *ERCC1* Gln504Lys, *ERCC4* Arg415Gln, *ERCC5* Asp1104His, *ERCC5* Cys526Ser, *ERCC6* Arg1230Pro, *ERCC6* Gln1413Arg, *XPC* Ala499Val and *XPC* Lys939Gln) on the individual susceptibility to non-familial thyroid cancer (manuscript in preparation), where we showed that patients carrying at least one variant allele of *CCNH* Val270Ala polymorphism seems to be at increased risk for thyroid cancer. To our knowledge, no other reports have been published trying to find susceptibility alleles in NER genes associating them with risk for thyroid cancer. One possible explanation for this is that the lesions produced by ionizing radiation are more likely to be repaired by BER, NHEJ and HR.

Several authors have described the increased incidence of a second malignancy in patients after diagnosis of thyroid cancer (Brown et al., 2008; Canchola et al., 2006; Garner et al., 2007; Verkooijen et al., 2006), pointing out breast cancer as the most frequent occurrence. However, some authors also considered the opposite, thyroid cancer being subsequent to breast cancer, suggesting the exposure to radiotherapy as the main cause of second malignancy in adjacent organs as a result of scattered radiation (Adjadj et al., 2003; Huang et

al., 2009). Furthermore, the incidence of other tumours might not represent a therapy effect but rather might be due to common risk factors. Therefore, the exposure to ionizing radiation and hormonal factors has been the risk factors well documented for both malignancies, although, there is no consensus in the results.

2.3 MMR – Mismatch repair

The Mismatch Repair (MMR) pathway plays a crucial role in repairing mismatches, which are small bulges in the DNA duplex, caused by small insertions, deletions or nucleotide substitutions in one strand of the duplex. Mismatches can be generated during DNA replication and repair. The failure of MMR leads to high mutation rates, microsatellite instability (MSI), losses of heterozygosity (LOH), reduction in apoptosis processes and increases in cell survival, as well as predisposition for carcinogenesis (Schofield & Hsieh, 2003; Schroering et al., 2007). MMR is also associated with an anti-recombination function, suppressing homologous recombination and plays a role in DNA-damage signaling (Smith et al., 2008).

The main MMR pathway is initiated by the recognition of a mismatch by the heterodimer consisting of the MSH2 and MSH6 proteins (also called MutSα). MutSα is responsible for the recognition of base mismatches and insertion/deletion loop (IDLs) in mono- to tetranucleotide repeats. This complex, MutSα, is able to recognize most base-base mismatches and short IDLs (Hsieh & Yamane, 2008).

Another MMR pathway, consisting of MSH2 and MSH3 heterodimers (MutSβ) is primarily responsible for binding to and correcting insertion/deletion mutations, preferentially dinucleotide and larger IDLs. Upon DNA mismatch recognition the repair process proceeds with the participation of the heterodimer consisting of MLH1 and PMS2 (also called MutLα), which acts as an endonuclease. Subsequent DNA excision, directed by strand breaks located either 5' or 3' to the mispair, is carried out by the exonuclease EXO1 (Hsieh & Yamane, 2008; Jiricny, 2006).

2.3.1 Mismatch repair and breast cancer

The *MSH2* gene is central in mismatch recognition and has been the most studied gene of MMR. There are several studies reporting mutations (Murata et al., 2002) and polymorphisms in several *MSH2* variants (Poplawski et al., 2005; Wong et al., 2008). Poplawski and colleagues showed a significant association between Gly322Asp polymorphism of the *MSH2* gene and breast cancer risk (Poplawski et al., 2005). However, another study of several families conducted by Wong and colleagues did not find any association between MSH2 and breast cancer (Wong et al., 2008). However, the scarcity of data about the involvement of polymorphisms in other MMR genes in breast cancer susceptibility, contributed to our MMR multigene study, which included *MSH3*, *MSH4*, *MSH6*, *MLH1*, *MLH3*, *PMS1* and *MUTYH* genes (Conde et al., 2009). Our results showed the potential involvement of Leu844Pro *MLH3* gene polymorphism in breast cancer susceptibility, as well as some SNP-SNP interactions. Different activities and functions of these genes as well as SNP variations may alter the level of repair, leading to higher rates of mutations and therefore an increase of breast cancer risk or conversely play a protective role in breast carcinogenesis.

2.3.2 Mismatch repair and thyroid cancer

To our knowledge, there are no data reporting the involvement of mismatch repair genes in thyroid cancer susceptibility.

2.4 DSB - Double strand breaks repair

Double-stranded breaks (DSBs) are the most injurious DNA damage. The failure to repair DSBs can result in chromosomal abnormalities, such as DNA translocations, that lead to cancerigenesis and are common in many cancers. DSBs can occur as a consequence of direct exposure to harmful exogenous agents, such as ionizing radiation, or by endogenous by-products of many metabolic processes, such as reactive oxygen species (ROS). They can also be generated during V(D)J recombination and when DNA single-strand breaks are encountered during DNA replication. The termini of chromosomes can also be recognized as DSB due to defective metabolism of telomeres. In order to face the threat of DSBs, prokaryotes and eukaryotes developed two mechanisms of repair, DNA end-joining and homologous repair.

DNA end-joining is the most straightforward repair mechanisms of DSBs, since it simply rejoins the broken ends regardless of the genetic consequences. There are two processes through which DNA end-joining can occur, non-homologous end-joining (NHEJ) and microhomology mediated end-joining (MMEJ). The first one is a Ku-dependent mechanism while the second one is Ku-independent. Both processes can maintain structural integrity, although, do not guarantee genetic integrity, being both error-prone and capable of generating new mutations. In NHEJ pathway, DNA ends are recognized and targeted by a heterodimeric Ku70/80 complex leaving the broken ends accessible for other factors. This DNA binding complex is important for recruitment of additional NHEJ proteins. Once bound to DNA, Ku proteins recruit the large DNA-dependent protein kinase catalytic subunit (DNAPKcs). The association of DNAPKcs-DNA-Ku complex activates the serine/threonine kinase activity of DNAPKcs contributing to the phosphorylation of the histone H2AX at lesion site and other factors such as nucleases. In case of incompatible ends, broken ends are processed by an endonuclease protein, named Artemis, trimming DNA overhangs and hairpins formed at the transition of double to single stranded DNA. Alternatively, the ssDNA tails can be filled in by polymerases (polμ and polλ). NHEJ repair is finalized by the complex XRCC4/LigaseIV that rejoins DNA ends. When broken DNA ends are not accessible for Ku proteins, due to other polypeptides covalently attached to DNA ends, the end joining occurs via Ku-independent pathway (MMEJ). The foremost distinguishing property of MMEJ is the use of 5–25 nucleotides sequences during the alignment of broken ends before joining, thereby resulting in larger deletions flanking the original break (Lieber, 2010; McVey & Lee, 2008).

In S-phase of cell cycle, there is a second copy of the genome, thus repair machinery can use this sister chromatid as template in order to achieve an error-free repair. This mechanism is known as homologous recombination repair (HR). In human cells, the early events are not completely understood, however the recruitment of the Mre11-Rad50-Nbs1 (MRN) complex and the phosphorylation of histone H2AX are two probable events, although these are not specific to HR since they can also occur, to a lesser extent, in NHEJ and MMEJ. Unlike end-joining repair, HR requires extensively resected broken ends to generate a 3′ single-stranded (ss) DNA tail. Firstly, MRN complex exposes both 3′ ends, the 3′ ssDNA tail is then stabilized by binding of RPA which facilitates the assembly of RAD51. With the help of RAD52 and BRCA2, a nucleoprotein filament is formed along the ssDNA tail and the search for homology in the sister chromatid by RAD51 is initiated. RAD51 catalyzes strand exchange during which ssDNA invades homologous duplex DNA forming a Holliday junction, which provides a primer to initiate new DNA synthesis, and a displacement loop (D-loop). Once the D-loop is formed, cells may undergo a process termed synthesis-

dependent strand annealing. The 3′ end in the D-loop is extended by repair synthesis and then the newly synthesized DNA strand dissociates to anneal to its original second strand to complete the reaction (Li & Heyer, 2008).

2.4.1 DSB and breast cancer

Linkage analysis of families with a high risk of breast cancer has identified two major susceptibility genes, *BRCA1* and *BRCA2*. The *BRCA1* and *BRCA2* genes are numerically the most important susceptibility genes for breast cancer, accounting for more than 80% of incidence in families with six or more cases of early-onset breast cancer. *BRCA1* tumours are typically invasive ductal carcinomas in which there is a high incidence of triple negative phenotype (negative for estrogen receptor, progesterone receptor and HER2). On the contrary, no distinctive histopathological phenotype has been described in *BRCA2* tumours. The main roles of the BRCA1 and BRCA2 are well known and are reviewed elsewhere (Gudmundsdottir & Ashworth, 2006).

Hereditary breast cancer only accounts for 5-10% of all cases (Dapic et al., 2005). Although high penetrance genes, such as *BRCA1* and *BRCA2*, can explain some of these cases, the sporadic cases are still not well understood and the search for susceptibility genes continues. The fact that two major hereditary breast cancer genes are involved in DSB repair pathway, point to the relevance of DSBs in sporadic breast cancer risk. Thus, due to the emergence of comprehensive high density maps of SNPs and affordable genotyping platforms, several genes involved in DSB repair have been genotyped in breast cancer patients, in order to found susceptibility alleles. The most studied genes are *NBS1*, *RAD51*, *XRCC2*, *XRCC3*, *BRCA1* and *BRCA2*. To a lesser extent, the NHEJ genes are also studied.

The *NBS1* gene codes for the protein NBS1 that participates in the MRN complex responsible for the DSB recognition and the early stages of the repair, as described above (Stracker & Petrini, 2011). Therefore, many studies were conducted in order to verify if a variant of this gene could be a susceptibility allele for breast cancer (Goode et al., 2002a; Kuschel et al., 2002; Lu et al., 2006; Millikan et al., 2005; Pooley et al., 2008; Silva et al., 2010; Smith et al., 2008; Zhang et al., 2005). The most studied SNPs were Asp399Asp, Glu185Gln, Leu34Leu and Pro672Pro. With the exception of Glu185Gln, all variants are synonymous, thus do not alter the conformational structure of the protein. No correlation was found between these polymorphisms and breast cancer. With the exception of a couple of studies (Lu et al., 2006; Smith et al., 2008), all results from studies in different populations regarding Glu185Gln were negative. Lu et al. found statistically significant association of the SNPs Glu185Gln and 5′ UTR 924T>C individually and haplotypes in young non-Hispanic white women in Texas, USA (Lu et al., 2006). Smith et al. showed that there were significant trends in breast cancer risk with increasing numbers of risk genotypes (at least one variant allele) of NBS1 185 GluGln/GlnGln in African-Americans (Smith et al., 2008). These discrepancies across studies might be associated with different genetic backgrounds, different risk factors in different populations, and the sample size of these studies. Thus, more studies are required in order to make any statement, although, according to the results obtained until now, *NBS1* is not a probable low penetrance gene.

The RAD51 protein is responsible for the central activity of the HRR pathway, in which it catalyses the invasion of the broken ends of the DSB into the intact sister chromatid. Among several polymorphisms in *RAD51* gene, a functional SNP at position 135 in 5′ UTR, changing a guanine to cytosine, was reported. Indeed, it was stated that this variant allele improves RAD51 expression (Hasselbach et al., 2005). Consequently, many molecular

epidemiological studies were performed with the purpose of examining an association between this *RAD51* variant and susceptibility to breast cancer. Many inconsistencies were found, even within the same population. Thus, a meta-analysis of all results found until now might bring some more precise estimation of the association of this SNP with susceptibility to breast cancer. Recently, four important meta-analyses (Gao et al., 2011; Sun et al., 2011; Wang et al., 2010; Zhou et al., 2011), covering tens of other studies and thousands of subjects, were unanimous to state that the variant allele of *RAD51* G135C may contribute to increased breast cancer susceptibility, which is in accordance with biological function study, which showed a more aggressive and poor prognosis phenotype (Costa et al., 2008). Zhou et al. also reported that the C variant of this SNP is associated with an augmented breast cancer risk among the *BRCA2* mutation carriers, but not *BRCA1* (Zhou et al., 2011). Therefore, taking into account these meta-analyses, *RAD51* G135C is a good candidate for a low penetrant risk factor for breast cancer. Recently, however, Yu et al. stated that these studies are not convincing since most are biased. According to the authors the populations have no representation of real general breast cancer cases since they took into account all breast cancer cases, including the *BRCA1* and *BRCA2* mutation carriers (Yu et al., 2011). The authors suggest that correct experimental design should be followed, such as subgroup meta-analysis in specific populations.

XRCC2 protein is a RAD51-related protein, essential for efficient HRR, and hence for maintenance of chromosome stability, making part of the nucleoprotein filament that acts as a cofactor for the RAD51 strand invasion and exchange activities, although there are other indications of its involvement in the late stages of the HRR pathway, namely the branch migration and Holliday junction resolution (Dudas & Chovanec, 2004). The *XRCC2* Arg188His polymorphism is by far the most studied in this gene. Many are in disagreement and contradictory, thus, recently, a meta-analysis was published by Yu et al. were all results published until then were analyzed and a more convincing and precise estimation of the association of this SNP and breast cancer was made (Yu et al., 2010). The authors reached the conclusion that XRCC2 Arg188His is not associated with individual susceptibility for breast cancer. However, they suggested that this SNP can modify the risk for breast cancer in response to exogenous compounds, and stressed the importance of investigating this possibility. Subsequent to this publication, a report made by us (Silva et al., 2010) was published with results concerning this SNP in a Portuguese population. The results were also negative when the SNP alone was considered, although, when the population was stratified according to the breast feeding status, it was observed that individuals that never breast fed and carried one variant allele of this polymorphism have a decreased risk for breast cancer. It is known that women that breast fed for long periods have a reduced risk for breast cancer. This can be explained by the fact that the exfoliation of ductal cells as a consequence of breast feeding might remove a significant number of cells with genetic damage, preventing their transformation into neoplastic cells. In those women that do not breast fed we have found a protective role of the variant allele of *XRCC2* Arg188His that might be related to a more efficient repair of DNA lesions. However, taking into consideration the size of our sample stratification, the small number of cases could act as a limitation factor. Thus, to exclude false positive results, further investigation in larger populations needs to be done.

XRCC3 protein is also a Rad51-related protein that participates in homologous recombination repair to maintain chromosome stability. XRCC3 forms filamentous structures in complex with Rad51C that assists RAD51-mediated strand invasion (Li &

Heyer, 2008). *XRCC3* is a highly polymorphic gene and many SNPs have been already described. Among them, *XRCC3* Thr241Met, 5'UTR A/G and IVS5-14 A/G are the most studied. As a result of inconclusive data of the several studies reported, four meta-analyses were published, three covering *XRCC3* Thr241Met (Economopoulos & Sergentanis, 2010; Garcia-Closas et al., 2006; Lee et al., 2007) and two the *XRCC3* 5'UTR A/G and IVS5-14 A/G (Garcia-Closas et al., 2006; Qiu et al., 2010a). In a first approach to obtain accurate results García-Closas et al. performed a meta-analysis with two populations, one from USA and other from Poland (Garcia-Closas et al., 2006). The authors concluded that the variant allele of these SNPs has a weak association with breast cancer. Later Lee et al. conducted a case-control with a Korean population and a meta-analysis of other 12 studies (Lee et al., 2007). The results fail to show statistically significant association of *XRCC3* Thr241Met with breast cancer. However the meta-analysis suggests a weak association between *XRCC3* Thr241Met and breast cancer, highlighting the differences between oriental and occidental populations. Recently, two more meta-analysis were published (Economopoulos & Sergentanis, 2010; Qiu et al., 2010a). Economopoulos & Sergentanis performed a meta-analysis concerning *XRCC3* Thr241Met and the results seems to be similar to those reported previously, thus, variant allele is associated with elevated breast cancer risk in non-Chinese subjects (Economopoulos & Sergentanis, 2010). Indeed, the authors have some reservations with regards to the studies with Chinese populations since no consistent data were obtained. Qiu et al., in order to fill a shortage of meta-analysis of *XRCC3* 5'UTR A/G and IVS5-14 A/G, published a report encompassing all eligible data from several studies concerning these two SNPs (Qiu et al., 2010a). The results suggest that the variant allele of *XRCC3* 5'UTR A/G is associated with breast cancer risk while the variant allele of *XRCC3* IVS5-14 A/G has a protective effect on breast cancer. Subsequently to these reports a work conducted by us (Silva et al., 2010) showed that *XRCC3* Thr241Met alone does not confer susceptibility to breast cancer. However, after stratification according to menopausal status, post-menopausal women carrying at least one variant allele seem to have lower risk for breast cancer, although stratifications applied to small populations could act as a limitation factor.

Along with *BRCA2, BRCA1* is well documented as a hereditary breast cancer susceptibility gene. However, there are much fewer published data addressing susceptibility alleles of BRCA1 in sporadic breast cancer (Cox et al., 2005; Freedman et al., 2005; Goode et al., 2002a; Huo et al., 2009). Of the four eligible reports, none showed association of common SNPs in *BRCA1* with breast cancer susceptibility. One report described a haplotype in *BRCA1* gene that may cause an increased risk for breast cancer, precisely, a 20% increment in risk for breast cancerigenesis. However, the authors failed to find out which variant is responsible for the association (Cox et al., 2005). Other study showed a possible association between an interaction of *BRCA1* and *ZNF350* with individual susceptibility for breast cancer (Huo et al., 2009). Similarly, *BRCA2* has few studies what concern sporadic breast cancer. However, a meta-analysis of about 44,903 subjects was recently published about *BRCA2* Asn372His polymorphism (Qiu et al., 2010b). This SNP is the most studied in this gene and according to the authors the variant allele may be a low-penetrant risk factor for breast cancer disease. However, the authors suggest that larger studies need to be done and homogeneous populations should be recruited, including well matched controls. Other meta-analysis also has reported the same results some years earlier (Garcia-Closas et al., 2006).Other study published by Ishitobi et al. reported null results for *BRCA2* Asn372His but not *BRCA2* Met784Val in a Japanese population. Specifically, the *BRCA2* Met784Val variant allele showed a significantly lower survival rate of 63% (Ishitobi et al., 2003).

To a lesser extent NHEJ genes were also studied. An early study found that the combined effect of individual SNPs of NHEJ genes may be significantly associated with breast cancer risk; indeed Fu et al. founded interesting results concerning estrogen exposure (Fu et al., 2003). The authors stated that women with greater putative high-risk genotypes have an increased risk for breast cancer disease and the results were even more significant and the risk stronger in women that never had a history of pregnancy. The authors also found statistically significant results for *Ku70* c.-1310 C>G and *XRCC4* Thr1394Gly individually. Later, Willems et al. also found similar results for the *Ku70* c.-1310 C>G SNP in a Belgian population (Willems et al., 2009). García-Closas et al. published a meta-analysis stating negative results for *LIG4* Asp568Asp, Thr9Ile and *XRCC4* IVS7-1A>G. Larger studies must be performed in order to verify these results and other populations should be taken into account (Garcia-Closas et al., 2006).

2.4.2 DSB and thyroid cancer

The only observed risk factor for thyroid cancer is ionizing radiation. However, most of cases do not have a history of ionizing radiation exposure and people exposed to X- or γ-rays, for example, not necessarily develop thyroid cancer. Thus, it is suggested that there might be an individual sensitivity to ionizing radiation due to genetic factors, such as polymorphic genes. Since ionizing radiation causes DSBs, is plausible to study SNPs in genes that are involved in the DSBs repair. Until now, few studies have been done concerning end-joining and homologous recombination repair. A study conducted by Bastos et al. observed that the coexistence of three or more variant alleles of *XRCC3* Thr241Met and *RAD51* 5'UTR (Ex1-59G>T) genes were associated with a significant higher risk for thyroid cancer (Bastos et al., 2009). However, independently the SNPs show no association with thyroid cancer. This SNP-SNP association might lead to a deficit in the formation of the DNA damage–induced RAD51 foci and consequently a deficient repair by HRR system. Sturgis et al. also reported a possible association of the variant allele of *XRCC3* Thr241Met with thyroid cancer (Sturgis et al., 2005). Indeed, among 10 SNPs studied, which include other SNPs of DSBs repair genes, such as *BRCA1*, *BRCA2*, *RAD51*, *XRCC3* and *XRCC7*, only the *XRCC3* Thr241Met seems to confer susceptibility for thyroid cancer. Further molecular epidemiological and functional studies must be performed in order to assure the accuracy of the results reported by both groups. Other study conducted by Gomes et al. shows a marginal association of NHEJ pathway SNPs with thyroid cancer (Gomes et al., 2010). To be precise, statically significant results were found for association of *Ku80* 3'UTR Ex21-238G>A and Ex21+338T>C SNPs with papillary tumours, after stratification by tumour type (papillary and follicular), showing that different histological types can have different genetic basis. This study seems to be the only one performed until now, concerning NHEJ and thyroid cancer.

3. Conclusion

Several reports have been published associating some SNPs in DNA repair genes with breast and thyroid cancer disease. Although relevant, the modifying effect of the majority of these SNPs in cell phenotype is still not understood and association studies are contradictory. This inconsistency might be due to different populations used, sample sizes, sample selection bias, genetic background and life style. Retrospective studies like these have to be interpreted with care and are difficult to draw meaningful practical conclusions from that can help directly patients with breast and thyroid cancer. In order to acquire more

powerful and accurate results several meta-analysis also have been published reviewing all studies made till publication date about a particular SNP and disease. Again, these reports need to be interpreted with caution, since many authors have study selection bias, including all cases of breast cancer, even the ones with *BRCA1* and *BRCA2* mutations carriers. Prospective studies and adequately selected meta-analysis should give further insight about the relevance of SNPs in breast and thyroid cancerigenesis.

Although the real role of SNPs in cancerigenesis is not well established by the authors, the new era in cancer treatment and prevention lies in the ability to treat patients individually according their genetic constitution and the DNA repair status of their tumours. For that, is crucial to have specific knowledge about the polymorphisms carried by each patient and how these polymorphisms influences response to therapy.

In fact, the existence of inter-individual variation influences response and survival rate following chemotherapy and radiation treatment of cancer. Standard cancer therapy involves the use of agents that themselves damage DNA with the ultimate goal of killing the cell. However, damaging the DNA does not always kill the cell, which is avoided by DNA repair pathways that remove the damage from DNA. Recent studies have suggested that the targeting of repair pathways by specific agents can result in effective killing of tumour cells (Li et al., 2010). DNA damage acquired from these treatments can initiate a number of cellular pathways involved in DNA repair, cell cycle control, metabolism and apoptosis (Bewick et al., 2011). If so, SNPs in genes of DNA repair may significantly affect its efficiency, clinical outcome and thus may help identify patients that can benefit from various treatments. Accordingly, new strategies for individualization of treatment in cancer patients are becoming an emerging issue.

Due to a phenomenon known as linkage disequilibrium, the value of a SNP in the same chromosome could be associated with specific values in other SNPs nearby. Indeed, specific SNPs associations (tagSNPs) related with the toxicity/efficacy of DNA damaging chemotherapy, improve our ability to map SNPs in specific genes associated with chemotherapy resistance and assure a better clinical outcome for cancer patients. This approach seems to be of importance since it can associate haplotype blocks with cancer therapy with lesser resources (Anunciação et al., 2010; Frazer et al., 2007).

Some SNPs in DNA repair genes have been reported as potential markers for individual susceptibility to breast (*e.g. XRCC1*; *XRCC2* and *XRCC3* genes polymorphisms) and thyroid (e.g. *XRCC1*; *XRCC3* and *RAD51* genes polymorphisms) cancers. However, the incoherent results don't have enough strength to demonstrate the real role of those SNPs, at least with regards to breast and thyroid carcinomas. We think that genetic polymorphisms, particularly SNPs, may have low influence in breast and thyroid cancerigenesis, however, SNPs may be much more relevant in acquired resistance to chemotherapeutic agents. In fact, new strategies for individualization of treatment in cancer patients are becoming an emerging issue. This approach must be the best way to find a practical result and clinical use for association studies. The emergence of SNPs with important roles in cancer therapy is now the focus of our work.

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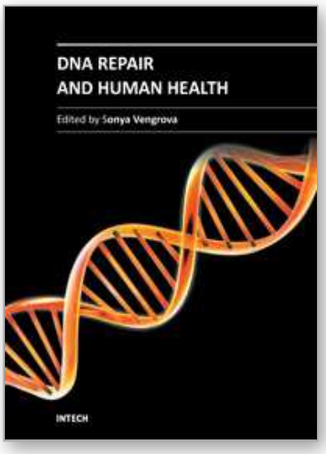

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Over the past decades, great advances have been made in understanding the cellular DNA repair pathways. At the same time, a wealth of descriptive knowledge of human diseases has been accumulated. Now, the basic research of the mechanisms of DNA repair is merging with clinical research, placing the action of the DNA repair pathways in the context of the whole organism. Such integrative approach enables understanding of the disease mechanisms and is invaluable in improving diagnostics and prevention, as well as designing better therapies. This book highlights the central role of DNA repair in human health and well-being. The reviews presented here, contain detailed descriptions of DNA repair pathways, as well as analysis of a large body of evidence addressing links between DNA damage repair and human health. They will be of interest to a broad audience, from molecular biologists working on DNA repair in any model system, to medical researchers.

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