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Review

Sporadic colorectal cancer and individual susceptibility: A review of the association studies investigating the role of DNA repair genetic polymorphisms

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Abstract

Mutations in one of the DNA repair genes are one of the most common reasons for cancer, and it may be assumed that the individual genetic background modulating the DNA repair capacity may affect the susceptibility to cancer. Numerous polymorphisms (mainly SNPs) have been identified for DNA repair genes, although their functional outcome and phenotypic effect is often unknown. The aim of the present review is to evaluate the studies investigating a possible influence of DNA repair polymorphisms in the risk of sporadic colorectal cancer and/or adenoma. Overall, no relevant common findings emerge among the studies, except for some statistically significant associations between polymorphisms in the *XRCC1* and *XPD* genes, mainly for colorectal adenoma risk. Other individual associations remain to be confirmed. This inconclusive data may suggest that the modulation of cancer risk depends not only on a single gene/SNP, but also on a joint effect of multiple polymorphisms (or haplotypes) within different genes or pathways, in close interaction with environmental factors. The relevance of many low-penetrance genes in cancer susceptibility is supposed to be very subtle. Several reviewed association studies revealed weaknesses in their design. However, there has been a progressive improvement over the years in aspects such as simultaneous genotyping and combined analyses of different polymorphisms in larger numbers of patients and controls, as well as stratification of results by ethnicity, gender, and tumor localization. This gained experience shows that only carefully designed studies of a sufficient statistical power may resolve the relationships between polymorphisms and colorectal cancer risk.

Keywords: Sporadic colorectal cancer; Individual susceptibility; DNA repair; Genetic polymorphisms; Single-nucleotide polymorphisms

Contents

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1. Introduction

1.1. Colorectal cancer: relevance and causes

Colorectal carcinoma (CRC) is one of the most frequent causes of cancer death in industrialized countries for both men and women, with a yearly incidence of about 50 new cases for every 100,000 people in the population [1]. The prevalence of CRC has been steadily increasing over the last century, while mortality rates have declined as a result of improved treatment and efficient screening and surveillance [2]. Stratification of the population into risk categories for CRC onset could enable targeted prevention, with measures tailored according to individual risk levels. To achieve this goal, relationships between individual genetic background and the relevance of non-genetic factors along with CRC pathogenesis need to be thoroughly explored [3,4].

CRC is traditionally divided into sporadic and familial (hereditary) forms [5] and represents a complex disease, whose development is determined by different combinations of genetic and environmental factors [8]. Genetic syndromes (familial adenomatous polyposis-FAP, Peutz-Jeghers syndrome, Juvenile polyposis and hereditary non-polyposis colon cancer-HNPCC) account for only 3% of all cases [7]. The majority of cases are sporadic or show a pattern of familial aggregation, not easily fitting into models of Mendelian inheritance [6]. Rare and highly penetrant mutations in cancer genes may act with little environmental influence, while a complex interplay of genetic and environmental factors is expected in the development of sporadic CRC. Several epidemiological studies have highlighted the role of diet and lifestyle in CRC risk in the last 40 years: positive correlations have been reported with the intake of fat, red meat and alcohol, as well as smoking [9,10], and inverse correlations with the intake of vegetables and fibres [11,12]. Other non-dietary environmental life-style and supplementary factors with protective effects include: high physical activity, hormone replacement therapy (HRT) in postmenopausal females, and the regular use of non-steroidal anti-inflammatory drugs (NSAIDs), such as aspirin [13,14]. Several of these associations (in particular for NSAIDs) are considered as consistent and biologically plausible; however, the causality is not fully understood. Sporadic CRC development requires a complex interaction between genetic and specific environmental/life style risk factors with different degrees of involvement. A net distinction between ‘genetic’ and ‘environmental’ predisposing factors is virtually impossible – a more realistic approach appears to be a continuum of risks contributing to sporadic CRC. CRC onset is likely to involve multiple genes with moderate effects (low penetrance type) and progress materializes due to aggressive gene-environment interactions [6,15].

1.2. Importance of low-penetrance genes in CRC

The identification of genetic polymorphisms (the occurrence in the same population of multiple discrete allelic states of which at least two have high frequency, conventionally of 1% or more) has stimulated hypotheses to explain the high degree of observed

individual variability in cancer susceptibility [16]. The successful sequencing of the human genome has provided the identification of a large number of low-penetrance alleles and molecular epidemiology has acquired the technological device for design large-scale case-control association studies. However, many results from epidemiologic studies have been inconsistent due to: (1) the small size of analyzed cohorts resulting in a low statistical power for detecting moderate effects, (2) false-positive results, (3) heterogeneity across study populations (ethnic differences in genetic background), (4) failure to consider effect modifiers such as environmental exposures, and (5) publication bias versus negative results [17]. In addition, mainly lacking in the association studies is the identification of biologically plausible functional reflections of many polymorphisms, as well as gene–gene and gene-environment interactions [18].

In the case of sporadic CRC, the number of relevant candidate genes with high-frequency low-penetrance alleles is wide [6,19]. A brief report of the main pathways follows.

1.2.1. Biotransformation

The general host metabolic status represents an important factor in modulating cancer progression [20]. Chen et al. [21] reported recently a meta-analysis on association studies between xenobiotic metabolism enzyme polymorphisms and CRC risk: *GSTT1* deletion appears as a main risk factor along with *NAT2*-rapid acetylator phenotype and genotype.

1.2.2. Methylation

Imbalanced DNA methylation, characterized by genomic hypomethylation and methylation of usually unmethylated CpG sites, is consistently observed in CRC [22]. *MTHFR* C677T and A1298C polymorphisms in the most important gene involved in DNA methylation and synthesis have recently been analyzed in association with adenoma and CRC risk. A decreased risk has been observed for carriers of the 677TT genotype, independently from the low/high folate status [23].

1.2.3. Immune response genes

Chronic inflammation is considered as a crucial factor in CRC development, since it affects key cellular processes like proliferation, adhesion, apoptosis, angiogenesis, and transformation. Cytokine-encoding genes influence inter-individual variation in the magnitude of inflammatory response, and variants of proinflammatory cytokines IL6, IL8, and IL10 have been associated with CRC risk [24–26]. Prostaglandin H synthase (*PTGS*) and peroxisome proliferator-activated receptor g (*PPARG*), were also studied in relation to CRC. A variant allele in the *PTGS2* promoter region has been associated with colorectal adenoma among non-NSAID users [27], while a nonsynonymous amino acid substitution in *PPARG* exon 12 has been associated with adenoma and CRC risk [24,28].

1.2.4. Oncogenes and tumor suppressor genes

Low-penetrance variants in high-penetrance genes might also be important in sporadic CRC. The *APC* I1307K polymorphism represents the strongest case for a susceptibility allele conferring increased CRC risk. The aminoacidic change does not alter the functional properties, but the underlying DNA sequence change (T → A) generates a short hypermutable poly-A repeat [29]. This mechanism increases the likelihood for occurrence of the first somatic hit (*APC* sequence frameshifts), affecting CRC risk. A higher frequency of *APC* 1307K variant has been reported among Ashkenazi descendants, corresponding to an approximately two-fold lifetime risk of CRC compared to the general population [30].

1.2.5. Cell cycle

The *Tp53* gene plays a fundamental role in preventing the replication of damaged DNA [31]. The most frequently studied *Tp53* R72P polymorphism provided conflicting results in relation to CRC [32,33]. Recently, Koushik et al. [34] have found an association of 72P allele with increased adenoma risk, suggesting R72P SNP being involved in the early stages of colorectal neoplasia and possibly in progression to invasive disease, depending on site and sex. Intronic sequences in *TP53*, regulate gene expression and DNA-protein interactions [35]. Intron 3 variant allele carriers showed a decreased CRC risk [32,33]. Cyclin D1 is a key cell cycle regulatory protein with altered expression and subcellular localization in human tumor cells. *Cyclin D1* A870G is associated with two distinct mRNA transcripts for G1/S regulatory protein [36], and results in conflicting associations with adenoma and CRC risk in several studies [37–40].

1.3. Possible role of DNA repair individual susceptibility

The genome is continuously attacked by endogenous and exogenous mutagens. Several responses follow DNA damage recognition to prevent replication in the presence of genetic errors: checkpoints activation to

arrest the cell cycle, transcription up-regulation to compensate for the damage, or apoptosis. Alternatively, the damage can be repaired at the DNA level enabling the cell to replicate. The maintenance of genomic integrity is thus of primary importance in the general and specialized functions of cells, as well as in the prevention of carcinogenesis [41,42].

Mutations in mismatch repair (MMR) genes are known to segregate in families with HNPCC [43]. In addition, the identification of germline mutations in base excision repair (BER) gene *MUTYH* in individuals with a predisposition to multiple colorectal adenomas and carcinomas has highlighted the relevance of DNA repair in CRC development [44]. Individual differences in DNA repair capacity pose an important issue in CRC etiology, despite still inadequate specific functional assays for assessing intra- and inter-individual variability [45]. The polymorphisms of genes involved in different DNA repair pathways may modulate the individual repair capacity in response to DNA damage, and may have an impact on individual genetic susceptibility to basically all types of cancer, including CRC [46]. The possible role of DNA repair individual susceptibility is schematically shown in Fig. 1. Over 520 amino acid substitution variants in 91 DNA repair genes have been identified in humans, while the number of other silent polymorphisms is constantly increasing, with many of them still unknown [47]. An analysis of SNPs in 88 DNA repair genes and their functional evaluation, based on the conservation of amino acids among the protein family members, shows that approximately 30% of variants of DNA repair proteins are likely to affect substantially the protein function [48]. For many polymorphisms, the functional significance/phenotypic changes are not experimentally proven in the general population. Few existing studies employed ionizing radiation sensitivity or cytogenetic challenge assay for evaluation of individual DNA repair capacity. Polymorphisms in *XRCC1* R194W and R399Q appear to modulate significantly markers of DNA and chromosomal damage [49,50] and these data seem to be biologically plausible [51]. Conflicting results have been reported on the impact of *OGG1* S326C [52–54], although this polymorphism seems to affect the glycosylase function due to the localization and phosphorylation status [55]. Recently, decreased irradiation-specific DNA repair rates were observed in cancer-free individuals with *XRCC1* 399QQ variant genotype, consistent with a role of the gene in BER pathway. In addition, the capacity to repair oxidative DNA damage was significantly decreased in individuals with *OGG1* 326CC variant genotype. Combined variant

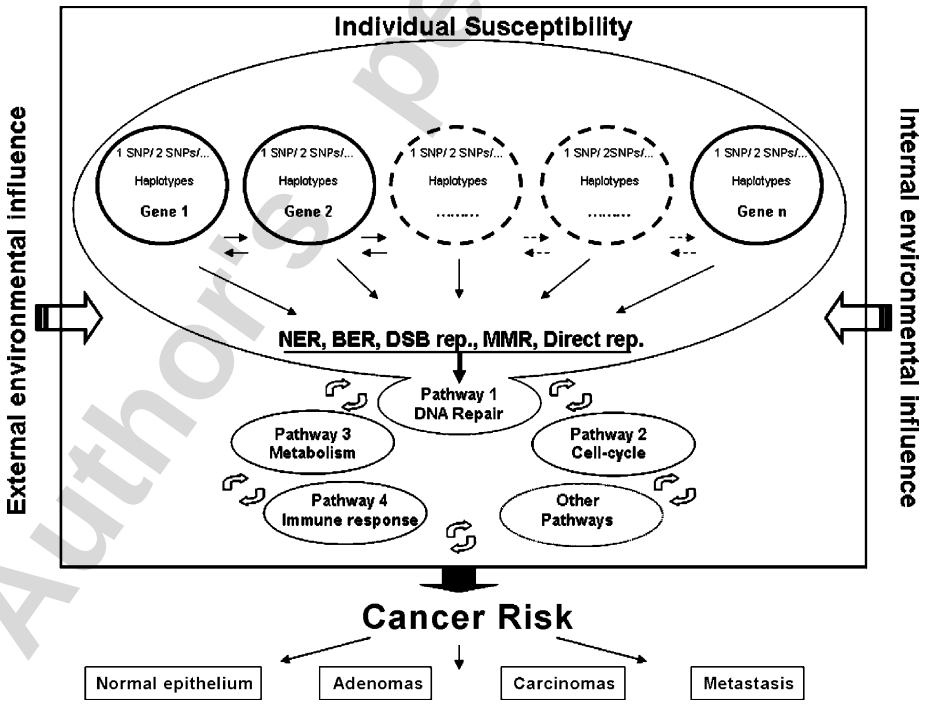

Fig. 1. The tentative role of individual genetic susceptibility along with external/internal environmental factors in sporadic CRC risk. Among several pathways potentially involved in the modulation of cancer development, due to the variability in their low-penetrance genes, a particular importance may be attributable to DNA repair. The individual DNA repair capacity, as evicted by the schema, is the result of complex interplay between genes of different DNA repair pathways, in which particular polymorphisms/haplotypes in combination may contribute to alter the ultimate functional activity and phenotypic outcome.

alleles of *XRCC1* R399Q, R194W and R280H and *APE1* D148E resulted in a decrease of irradiation-specific repair rates, reflecting a SNP-SNP interaction. Combined variant alleles of *OGG1* S326C and *APE1* D148E decreased the repair of DNA oxidative damage as well [56]. The above studies may contribute to the more meaningful choice of genes/polymorphisms for association studies. Several reviews have recently tried to summarize the main results of the studies on DNA repair genetic polymorphisms in association with cancer [54,57–60]. However, the outcomes from epidemiological studies are ambiguous. Only in the case of *OGG1* and *XRCC1* for BER and *XPD* for nucleotide excision repair (NER), consistent evidences for association of particular genetic polymorphisms with specific cancers have been found. *OGG1* S326C variant allele seems to be associated with increased risk of lung, esophagus, and prostate cancer [54,57,58], while SNPs of *XPD* have been associated with skin, breast and lung cancer [59,60].

In the case of CRC, association studies with DNA repair polymorphisms have not yet been comprehensively and critically reviewed. In order to enable an understanding of the current knowledge, the following paragraphs will analyse in detail all association studies available on DNA repair polymorphisms and sporadic CRC.

2. Methods

We reviewed a total of 25 association studies between DNA repair polymorphisms and haplotypes and risk of CRC. We evaluated available studies from Pub Med (http://www.ncbi.nlm.nih.gov/), without any exclusion. Among these studies, a few considered individuals with both adenomas and sporadic CRC, or with adenomas only. We also included these studies, since adenomas are considered important precursors of CRC. SNPs addressed in the reviewed studies are listed in Table 1. They are organized by DNA repair pathways in which the corresponding genes are involved. Table 1 provides, whenever possible, frequencies for the variant allele in the

Table 1
Description of DNA repair polymorphisms investigated in the studies reviewed

DNA repair pathway	Gene (alias)	Polymorphism	Position and base change	Variant allele frequency in controls[a]
NER	*XPD* (*ERCC2*)	IVS19-70	IVS19-70, G → A	0.29
		D312N	Ex 10, G → A	0.33–0.37
		K751Q	Ex 23, A → C	0.07–0.39
		R156R	Ex 6, C → A	0.39
		D711D	Ex 22, C → T	0.36
	XPF (*ERCC4*)	P379S	Ex 7, C → T	0.001–0.004
		R415Q	Ex 8, G → A	0.07–0.11
		E875G	Ex 11, A → G	n.a.
		Codon 824 (?)[b]	Ex 11, T → C	0.14
		S662P	Ex 10–34, T → C	0.003
	XPG (*ERCC5*)	M254V	Ex 7, A → G	0.03
		335 T → C (H46H)	Ex 2, T → C	0.4
		C529S	Ex 8, G → C	0.04–0.05
		D1104H	Ex 15, G → C	0.21–0.28
	XPC	R492H	Ex 8, G → A	0.06
		A499V	Ex 8, C → T	0.23–0.24
		R687R	Ex 11 + 28, G → A	0.27
		K939Q	Ex 16, A → C	0.40–0.42
	RAD23B (*hHR23B*)	A249V	Ex 7, C → T	0.17–0.20
	CSB (*ERCC6*, *RAD26*)	M1097V	Ex 18, A → G	0.19–0.21
		R1230P	Ex 18, G → C	0.10–0.11
		Q1413R	Ex 21, A → G	0.19
		R1213G	Ex18-142, A → G	0.20
	CCNH (*CAK*)	V270A	Ex 8, T → C	0.20
	ERCC1 (*UV20*)	19716 C → G	IVS3 + 74, C → G	0.35–0.37
		19007 T → C (N118N)	Ex 4, T → C	0.38
		17677 A → C	IVS5 + 33, A → C	0.11
		15310 G → C	G → C	0.08
		8092 C → G	IVS9-103, C → G	0.23

Table 1 (*Continued*)

DNA repair pathway	Gene (alias)	Polymorphism	Position and base change	Variant allele frequency in controls[a]
		(?)[b]	Ex 4, G → A	0.40
		Q504K	196 bp 3′ of STP, T → G	0.26
	XPA (*XP1*)	3′UTR C → G	Ex 6-327, C → G	Rare
	XPB (*ERCC3*)	487 bp 3′ of STP, G → A	487 bp 3′ of STP, G → A	0.36
		IVS6-108, A → C	IVS6-108, A → C	0.34
	RPA2	3′UTR T → C	Ex 9-51, T → C	0.36
	LIG1	5′UTR C → T	Ex 2-24, C → T	0.13
BER	*OGG1* (*MUTM*)	R154H	G → T	0.003
		S326C	Ex 6, C → G	0.19–0.52
	XRCC1	R194W	Ex 6, C → T	0.05–0.32
		R280H	Ex 9, G → A	0.02–0.09
		R399Q	Ex 10, G → A	0.14–0.39
		Q632Q	Ex 17, G → A	0.42
	LIG3	K811T	Ex 15, A → C	0.002
		R780H	Ex 18, G → A	0.002
	APEX (*APE1*)	Q51H	Ex 3, G → C	0.03
		D148E	Ex 5, T → G	0.45
	POLB	P242R	Ex 12, C → G	0.01
	PCNA	1876 A → G	A → G	0.13
	MUTYH	Y165C	n.a.	Rare
		G382D	n.a.	0.01
DSB Repair	*XRCC3*	T241M	Ex 8, C → T	0.02–0.45
		4541 A → G	A → G	0.19
		17893 A → G	A → G	0.32
	NBS1 (*NBN*, *ATV*) *XRCC2*	E185Q	Ex 5, C → G	n.a.
	XRCC9 (*FAG*, *FANCG*)	R188H	Ex 3, G → A	0.07–0.09
		T297I	Ex 7, C → T	0.009
Direct repair	*MGMT*	L84F	Ex 2, C → T	0.12–0.14
		171 C → T (L53L)	Ex 2, C → T	0.13
		I143V	Ex 4, A → G	0.10–0.12
Mismatch repair	*EXO1*	T439M	Ex 12, C → T	0.10
		P757L	Ex 15, C → T	0.46
	MLH1 (*HNPCC2*)	−93 G → A	Promoter G → A	0.22
		I219V	Ex 8, A → G	0.03–0.33
		V384D	Ex 12, T → A	0.03
	hMSH3	T1036A	Ex 23 + 3G → A	0.28
		R940Q	Ex 21, G → A	0.15
	hMSH2 (*HNPCC1*)	L390F	Ex 5, C → T	0.02
		IVS12	IVS12, C → T	0.4
	hMSH6 (HNPCC5)	G39E	Ex 1 G → A	0.17–0.18
		V509A	Exon 4, T → C	Rare
		−159 C → T	Promoter, C → T	0.01

[a] Frequency of variant allele among control populations in association studies cited in this review.
[b] The polymorphisms were not fully identified from the related studies.

Table 2
Association studies between genetic polymorphisms in **NER** genes and risk of CRC/adenomas

Reference	Genes (polymorphisms)	Cases	Controls	Ethnicity (country)	Associations	Interactions
Berndt et al. [62]	*XPA* (3′UTR C → G) *XPB* (487 bp 3′ of STP, G → A, IVS6-108, A → C) *XPC* (R492H, A499V, R687R, K939Q) *XPD* (K751Q, IVS19-70) *XPF* (R415Q, S662P) *XPG* (C529S, D1104H) *CSB* (M1097V, R1213G, R1230P) *LIG1* (5′UTR C → T) *ERCC1* (Q504K, 19716 C → G) *RAD23B* (A249V) RPA2 (3′UTR T → C)	250 carcinomas	2224 no history of cancer	American mixed (Caucasian 98%) (USA)	*CSB* 1097V and 1213G alleles associated with ↑ CRC risk *XPC* 492H allele associated with ↑ CRC risk *XPC* haplotype containing 492H allele associated with ↑ CRC risk	SNP-SNP interaction between *CSB* 1097V and *XPC* 492H alleles and *CSB* 1213G and *XPC* 492H alleles slightly ↑ CRC risk *CSB* 1097V and 1213G alleles associated with ↑ CRC risk among individuals with a first-degree relative with CRC No interactions with age at diagnosis, gender, smoking habit, red meat intake, folate intake, and body mass index
Goodman et al. [64]	*XPD* (D312N) *XPF* (R415Q, E875G) *XPG* (C529S, D1104H)	216 carcinomas (males)	255 no history of cancer (males)	Caucasian and African American (USA)	No association of single SNP	No interactions between NER (or other DNA repair) polymorphisms
Huang et al. [72]	*XPD* (D312N, K751Q) *XPC* (R492H, A499V, K939Q) *RAD23B* (A249V) *CSB* (M1097V, R1230P, Q1413R) *CCNH* (V270A) *XPF* (P379S, R415Q) *XPG* (M254V, C529S, D1104H)	772 high-risk adenomas	777 negative to colonscopy screening	American mixed (USA)	No association of single SNP	Smokers with *XPC* haplotype (R, A, and Q) associated with ↑ risk of high-risk adenomas No interactions with age, gender, and ethnicity
Moreno et al. [63]	*ERCC1* (19716 G → C, 19007 T → C, 17677 A → C, 15310 G → C, 8092 C → A) *XPD* (D312N, K751Q) *XPF* (P379S, R415Q) *XPG* (335 T → C)	377 carcinomas	329 hospital healthy	Caucasian (Spain)	*ERCC1* 17677C allele associated with ↑ CRC risk in an additive model *ERCC1* haplotype (19716C, 19007C and 17677C) associated with ↑ CRC risk	No interactions with age
Skjelbred et al. [70]	*XPD* (K751Q)	157 carcinomas 983 adenomas (227 high-risk and 756 low-risk)	399 negative to colonscopy screening	Caucasian (Norway)	*XPD* 751Q allele associated with ↑ risk of low-risk adenoma	No interactions with smoking habit

Skjelbred et al. [71]	*ERCC1* (N148N)	156 carcinomas 981 adenomas (227 high-risk and 754 low-risk)	399 negative to colonscopy screening	Caucasian (Norway)	No association of single SNP	No interactions with smoking and alcohol habits
Bigler et al. [73]	*XPD* (D312N, K751Q) *XPG* (D1104H)	694 (384 adenomatous polyps, 191 hyperplastic polyps, 119 both types)	621 negative to colonscopy screening	Afroamerican and Caucasian (USA)	No association of single SNP Combination of *XPD* 312N and 751Q alleles associated with ↑ adenoma risk *XPG* 1104HH genotype associated with ↓ risk of hyperplastic polyps	Heavy smokers with *XPD* combined homozygous variant genotypes or *XPG* 1104DD genotype had an ↑ risk of adenomatous polyps *XPG* 1104HH genotype associated with ↓ risk of hyperplastic polyps in young individuals (<60 years) No interactions with gender, meat consumption, and alcohol and vitamin intakes
Starinsky et al. [68]	*XPD* (K751Q)	456 carcinomas	87 hospital healthy	Jewish (64% Ashkenazi) (Israeli)	No association of single SNP	*XPD* 751Q allele associated with age at diagnosis in Ashkenazi subset only
Yeh et al. [65–67]	*XPD* (K751Q)	727 carcinomas	736 negative to colonscopy screening	Asian (Taiwan)	No association of single SNP	↑ CRC risk for combinations of *XPD, XRCC3*, and *XRCC1* genotypes with OR > 1, particularly for younger individuals (<61 years) and for rectum cases Combinations of *XPD* and *CYP1A1*2C* and *GSTT1* deletion high-risk genotypes associated with ↑ CRC risk No interactions for *XPD* polymorphism with smoking habit, alcohol and meat intake, or vegetable/fruit and fish/shrimp consumption
Mort et al. [69]	*XPD* (exon 6, exon 22, K751Q) *ERCC1* exon 4 *XPG* (D1104H) *XPF* (E875G)	45 carcinomas	71 hospital healthy (not for all genes)	Caucasians (?) (England)	No association of single SNP	

(?) Not fully specified in the study.

Table 3
Association studies between genetic polymorphisms in **BER** genes and risk of CRC/adenomas

Reference	Genes (polymorphisms)	Cases	Controls	Ethnicity (country)	Associations (main results)	Interactions
Goodman et al. [64]	*OGG1* (S326C) *XRCC1* (R194W, R399Q)	216 carcinomas (males)	255 no history of cancer (males)	Caucasian and African American (USA)	Significant P_{trend} for *OGG1* (S326C)	No interactions between BER (or other DNA repair) polymorphisms
Moreno et al. [63]	*OGG1* (S326C) *LIG3* (K811T, R780H) *APEX* (Q51H, D148E) *POLB* (P242R) *XRCC1* (R194W, R280H, R399Q) *PCNA* (1876 A → G) *MUTYH* (Y165C, G382D)	377 carcinomas	329 hospital healthy	Caucasian (Spain)	*OGG1* 326C allele associated with ↑ CRC risk *POLB* 242R rare allele associated with ↓ CRC risk (no homozygous variant found)	*OGG1* 326CC genotype associated with ↑ CRC risk in young individuals *XRCC1* 194W and 280H minor alleles associated with a ↓ CRC risk in young individuals
Skjelbred et al. [70]	*XRCC1* (R194W, R280H, R399Q)	157 carcinomas 983 adenomas (227 high-risk and 756 low-risk)	399 negative to colonscopy screening	Caucasian (Norway)	*XRCC1* 280H allele associated with ↑ adenoma risk *XRCC1* 399Q allele associated with ↓ risk in the high-risk adenoma group	No interaction with smoking habit
Hansen et al. [78]	*OGG1* (S326C)	166 carcinomas 974 adenomas	397 negative to colonscopy screening	Caucasian (Norway)	*OGG1* 326C allele associated with ↓ carcinoma risk	
Hong et al. [40,74]	*XRCC1* (R194W, R280H, R399Q)	209 carcinomas	209 hospital healthy	Asian (South Korea)	*XRCC1* 399Q allele associated with ↑ CRC risk The combined alleles *XRCC1* 194W-280R-399Q associated with ↑ CRC risk	↑ CRC risk associated with alcohol intake in combined alleles 194W-280R-399R, 194W-280H-399R and 194R-280R-399Q No interaction with smoking, dietary habits and physical activity
Stern et al. [79]	*XRCC1* (R194W, R399Q)	753 adenomas	799 hospital healthy	Caucasian, African American, Latinos, Asian/Pacific Island (USA)	*XRCC1* 399QQ genotype associated with ↓ adenoma risk	↑ Adenoma risk associated with high monounsaturated fatty acid intake, in individuals with *XRCC1* 194RR and 399QQ combined genotypes

					XRCC1 194RR and 399QQ combined genotypes associated with ↓ adenoma risk	No interaction with polyunsaturated fatty acid intake and antioxidant intake
Yeh et al. [65–67]	*XRCC1* (R399Q)	727 carcinomas	736 negative to colonscopy screening	Asian (Taiwan)	No association of single SNP	*XRCC1* 399R allele associated with ↑ CRC risk for young individuals (<61yrs) and for rectum cases ↑ CRC risk for combinations of *XRCC1*, *XPD* and *XRCC3* genotypes, particularly for younger individuals (<61yrs) and for rectum cases No interactions with smoking habit, alcohol and meat intake, or vegetable/fruit and fish/shrimp consumption
Kim et al. [80,86]	*OGG1* (R154H)	500 carcinomas	527 hospital healthy	Asian (South Korea)	*OGG1* 154H allele associated moderate ↑ CRC risk	
Krupa and Blasiak [77]	*XRCC1* (R399Q)	51 carcinomas	100 hospital healthy	Caucasian (Poland)	*XRCC1* 399Q allele (?) weakly associated with ↑ CRC risk	Gene–gene interaction between the *XRCC3* 241MM and the *XRCC1* 399RR genotypes slightly ↑ CRC risk
Kim et al. [76]	*OGG1* (S326C)	125 carcinomas	247 cancer-free	Asian (South Korea)	No association of single SNP	*OGG1* 326CC genotype associated with ↑ CRC risk in group with higher meat intake Smokers with *OGG1* 326CC genotype moderately associated with ↑ CRC risk No interactions with alcohol consumption, vegetable and soybean intake, physical activity and family history of cancer

Table 3 (*Continued*)

Reference	Genes (polymorphisms)	Cases	Controls	Ethnicity (country)	Associations (main results)	Interactions
Mort et al. [69]	*XRCC1*, exon 17	45 carcinomas	71 hospital healthy (not for all genes)	Caucasian (?) (England)	No association of single SNP	
Abdel-Rahman et al. [75]	*XRCC1* (R194W, R399Q)	48 carcinomas	48 healthy population	(?) (Egypt)	*XRCC1* 399Q allele associated with ↑ CRC risk	*XRCC1* 399Q allele associated with ↑ CRC risk only in young individuals (<40 years), and mainly in urban resident individuals

(?) Not fully specified in the study.

control population to facilitate the comparisons among studies. Results section and Tables 2–6 are organized according to the different DNA repair pathways and summarize main characteristics and main outcomes of reviewed epidemiological studies. They are listed chronologically. Some of the studies analyzed simultaneously several polymorphisms in different DNA repair pathways, sometimes evaluating the results from polymorphisms in combination: in this case, studies were reported separately for each DNA repair pathway and the overlapping outcomes were specified. The main interactions with confounders were also highlighted from each study and reported in Tables 2–6. Present review focuses primarily on the association with DNA repair SNPs, while stressing an importance of gene-environmental interactions in the future studies.

The comparative funnel plots (Figs. 2–4) were constructed for SNPs (*XPD* K751Q, *XRCC1* R399Q and *XRCC3* T241M) most frequently studied for associations with adenoma or CRC risk. We included the crude odds ratios (OR) for the homozygous variant genotype, considering the homozygous wild-type genotype as the referent. A brief section was dedicated to the studies investigating the relationship between individual susceptibility in DNA repair genes and the prognosis and efficacy/toxicity of the therapy for CRC. The field of the pharmacogenetics, although scarcely explored currently, may be of interest in understanding the role of DNA repair polymorphisms in the secondary prevention to this type of cancer.

3. Results

3.1. Nucleotide excision repair (NER)

The NER pathway is the most versatile mechanism of DNA repair, removing a large number of structurally unrelated DNA lesions: bulky lesions such as pyrimidine dimers, other photoproducts, larger chemical adducts, and cross-links. Two distinct NER subpathways have been recognized: global genome NER, detecting and removing lesions throughout the whole genome, and transcription-coupled NER, ensuring the fastest repair of lesions located on the transcribed strand of actively transcribed genes. The NER pathway involves at least four steps: (a) damage recognition by a complex of bound proteins including XPC; (b) unwinding of the DNA by the TFIIH complex that includes XPD; (c) removal of the damaged single-stranded fragments (usually about 27–30 bp) by molecules including an ERCC1 and XPF complex; and (d) synthesis by DNA polymerases [46,61].

The complete list of NER genes and polymorphisms investigated in all reviewed association studies on adenoma and CRC risk is available in Table 1. In Table 2, the 12 studies evaluating one or more polymorphisms of NER genes are described.

Table 4
Association studies between genetic polymorphisms in **Double-strand break repair** genes and risk of CRC/adenomas

Reference	Genes (polymorphisms)	Cases	Controls	Ethnicity (Country)	Associations (Main results)	Interactions
Goodman et al. [64]	*XRCC3* (T241M) *NBS1* (E185G)	216 carcinomas (males)	255 no history of cancer (males)	Caucasian and African American (USA)	No association of single SNP	No interactions between DSB (or other DNA repair) polymorphisms
Skjelbred et al. [70]	*XRCC3* (T241M)	157 carcinomas 983 adenomas (227 high-risk and 756 low-risk)	399 negative to colonscopy screening	Caucasian (Norway)	No association of single SNP	No interactions with smoking habit or alcohol consumption
Moreno et al. [63]	*XRCC2* (R188H) *XRCC3* (T241M) *XRCC9* (T297I)	377 carcinomas	329 hospital healthy	Caucasian (Spain)	No association of single SNP	No interaction with age
Jin et al. [83]	*XRCC3* (T241M)	140 carcinomas	280 cancer-free	Asian (China)	*XRCC3* 241M allele associated with ↑ CRC risk	*XRCC3* 241M allele in older individuals associated with ↑ CRC risk Non smokers and non using alcohol individuals with *XRCC3* 241M allele associated with ↑ CRC risk No interaction with gender
Stern et al. [79]	*XRCC3* (T241M)	753 adenomas	799 hospital healthy	Caucasian, African American, Latinos, Asian/Pacific Island (USA)	No association of single SNP	No interactions with poly and mono unsaturated fatty acids and antioxidant intake
Yeh et al. [65–67]	*XRCC3* (T241M)	776 carcinomas	736 negative to colonscopy screening	Asian (Taiwan)	No association of single SNP	*XRCC3* 241T allele associated with ↑ CRC risk in low meat consumption individuals, particular in rectum cases ↑ CRC risk for combinations of *XRCC3*, *XPD* and *XRCC1* genotypes with OR >1, particularly for younger individuals (<61yrs) and for rectum cases Combinations of *XRCC3* T241M and *CYP1A1**2C high-risk genotypes associated ↑ CRC risk in women No interactions with smoking habit, alcohol intake and vegetable/fruit and fish/shrimp consumption

Table 4 (*Continued*)

Reference	Genes (polymorphisms)	Cases	Controls	Ethnicity (Country)	Associations (Main results)	Interactions
Krupa et Blasiak [77]	*XRCC3* (T241M)	51 carcinomas	100 hospital healthy	Caucasian (Poland)	*XRCC3* 241MM genotype strongly associated with ↑ CRC risk	Gene–gene interaction between *XRCC3* 241MM and *XRCC1* 399RR genotypes slightly ↑ CRC risk
Tranah et al. [84]	*XRCC2* (R188H), *XRCC3* (T241M, 4541 A → G, 17893 A → G)	932 adenomas	1282 cancer-free	Caucasian (?) (USA)	No association of single SNP	No interactions of alcohol and smoking habit, although both confounders increased OR of genotypes No interactions with plasma and dietary folate
Mort et al. [69]	*XRCC3* (T241M)	123 carcinomas	128 hospital healthy	Caucasian (?) (England)	Moderate association of T241 allele with ↑ CRC	

(?) Not fully specified in the study.

Berndt et al. [62] analysed very recently a total of 22 polymorphisms in 11 genes involved in NER pathway in 250 CRC cases and 2224 controls. The *CSB* 1213G and 1097V variant alleles were associated with a dose-dependent increased risk of cancer in comparison with the wild-type ($P = 0.0005$ and $P = 0.001$, respectively). Both SNPs were found to be in strong linkage disequilibrium ($D' = 1.0$), so the effect of one polymorphism was not discernable from the other. *XPC* 492H variant allele was also associated with increased CRC risk ($P = 0.004$) and haplotype analyses for four *XPC* SNPs showed an association with CRC risk only when 492H variant allele is present. *CSB* R1213G and *XPC* R492H in combination revealed an increased CRC risk followed increasing number of variant alleles ($P_{trend} = 0.00003$). Although the study was performed on a cohort of mixed Americans, the authors stated that Caucasians represented 98% of the population and also considered ethnicity in the statistics.

Moreno et al. [63], investigated polymorphisms of genes involved in several DNA repair pathways, in a Spanish cohort of 377 CRC cases and 329 controls. The authors considered a total of 10 polymorphisms in four NER genes and they found a borderline association with CRC risk for *ERCC1* 17677 A → C ($P = 0.058$) in an additive model (i.e. combining variant + heterozygous). The risk for selected *ERCC1* haplotypes (19716 G → C, 19007 T → C, 17677 A → C, 15310 G → C, 8092 C → A) was also tested. The haplotype containing the minor allele C of *ERCC1* 17677 A → C was significantly associated with increased risk of CRC when compared with the most frequent haplotype (OR, 2.32; 95% CI, 1.01–5.34). For all other NER polymorphisms analysed, no other associations were observed.

Goodman et al. [64], exploring SNP-SNP interactions and colon cancer risk, investigated 94 genes in several pathways potentially involved in cancer development. The authors developed a statistical polymorphism interaction analysis to screen the most important SNPs combinations. Among different DNA repair polymorphisms, they investigated five SNPs in three NER genes (*XPD, XPF* and *XPG*) in 216 cases and 255 controls (males only), but no association was found with cancer risk. The study is interesting for the idea to investigate a large set of SNPs and their possible interactions, reflecting the real situation in the organism. However, the size of the population is rather limited for this kind of analysis and the study included different ethnicities (Caucasian and Afro-American), precluding robust outcomes.

Two studies by Yeh and co-workers [65,66] analyzed a cohort of 727 CRC patients and 736 controls from

Table 5
Association studies between genetic polymorphisms in **Mismatch repair** genes and risk of CRC/adenomas

Reference	Genes (polymorphisms)	Cases	Controls	Ethnicity (country)	Associations (main results)	Interactions
Berndt et al. [85]	*hMLH1* (I219V) *hMSH3* (T1036A, R940Q)	237 carcinomas	2189 no history of cancer	American mixed (Caucasian 98%) (USA)	*hMSH3* 1036A allele associated with ↑ CRC risk *hMSH6* 39EE genotype associated with ↑ risk of rectal cancer	*hMSH3* 1036A allele associated with ↑ risk of CRC in interaction with processed meat intake ≥10 g/day *hMSH3* haplotype containing 1036A allele associated with ↑ CRC risk among individuals with processed meat intake ≥10 g/day
	hMSH6 (G39E)				*hMSH3* haplotype containing both 940Q and 1036A alleles associated with ↑ CRC risk	No interactions with gender, smoking habit, folate intake, and alcohol consumption, and family history
Yu et al. [87]	*hMLH1* (−93G → A, I219V) *hMSH6* (G39E)	719 (401 adenomas, 195 hyperplastic polyps, 123 both types)	624 negative to colonscopy screening	Caucasian-American (97%) (USA)	No association of single SNP	*hMLH1*−93 A allele is associated with ↑ risk of hyperplastic polyps associated with smoking
Yamamoto et al. [89]	*EXO1* (T439M, P757L)	102 carcinomas	110 healthy population	Asian (Japan)	*EXO1* 439M allele associated with ↑ CRC risk *EXO1* 757 LL genotype associated with ↓ CRC risk *EXO1* 439MM and 439TM, with *EXO1* 757PL genotypes are associated with ↑ CRC risk	
Kim et al. [80,86]	*hMLH1* (I219V, V384D) *hMSH2* (L390F, gIVS12)	107 carcinomas	330 healthy controls and 107 first degree relatives of cases	Asian (Korea)	No association of single SNP	
Peterlongo et al. [90]	*hMSH6* (V509A, −159 C → T)	167 carcinomas	190 healthy controls	American Jews (USA)	No association of single SNP	

Table 6
Association studies between genetic polymorphisms in *MGMT* gene (**Direct repair**) and risk of CRC/adenomas

Reference	Genes (polymorphisms)	Cases	Controls	Ethnicity (country)	Associations (main results)	Interactions
Goodman et al. [64]	*MGMT* (171 C → T)	216 carcinomas (males)	255 no history of cancer (males)	Caucasian and African American (USA)	No association of single SNP	No interactions between MGMT and other DNA repair polymorphisms
Moreno et al. [63]	*MGMT* (171 C → T, L84F, I143V)	377 carcinomas	329 hospital healthy	Caucasian (Spain)	No association of single SNP	No interactions with age
Bigler et al. [73]	*MGMT* (L84F, I143V) *MGMT* (L84F, I143V)	694 (384 adenomatous polyps, 191 hyperplastic polyps, 119 both types)	601 negative to colonscopy screening	African American and Caucasian (USA)	No association of single SNP	*MGMT* combined genotypes showed an interaction with smoking habit No interactions with age, gender, meat consumption, and alcohol and vitamin intake
Tranah et al. [93]		197 carcinomas (females) 451 carcinomas (males)	2500 cancer-free (females) 451 cancer-free (males)	Caucasian-American (97%) (USA)	*MGMT* 143V allele associated with ↓ risk of CRC in cohort of women No association of single SNP in men cohort	*MGMT* 84F allele associated with ↑ risk of CRC among women consuming ≥0.5 drink/day. No interaction between alcohol intake and *MGMT* I143V polymorphism *MGMT* 84F and 143V alleles associated with ↓ risk of CRC among women with BMI ≥25 *MGMT* 84LL genotype and use of postmenopausal hormone associated with ↑ risk of CRC No interactions with smoking habit, folate, and processed meat intake in women No interactions with BMI, alcohol consumption, and smoking history in men

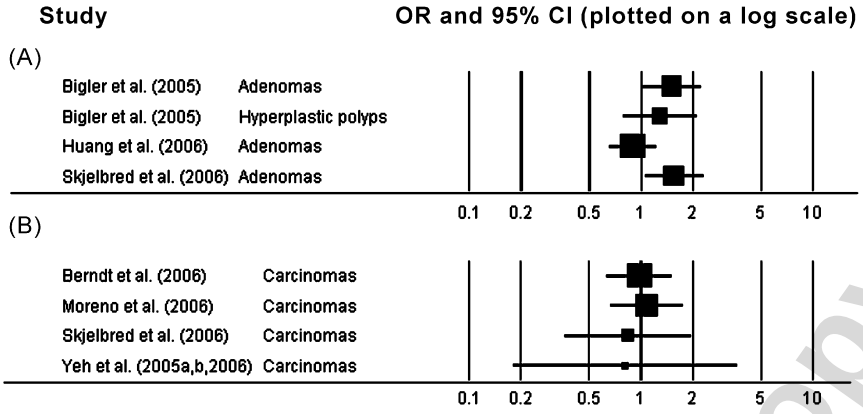

Fig. 2. Odds ratios for the relation between *XPD* K751Q polymorphism, adenoma (A) and CRC (B) risk in the reviewed studies. For each study, the odds ratio for the homozygous variant genotype estimated is plotted with a box, and the area of each box is inversely proportional to the variance of the estimated effect. Horizontal lines show 95% confidence interval. Individuals with homozygous wild-type genotype represent a referent group.

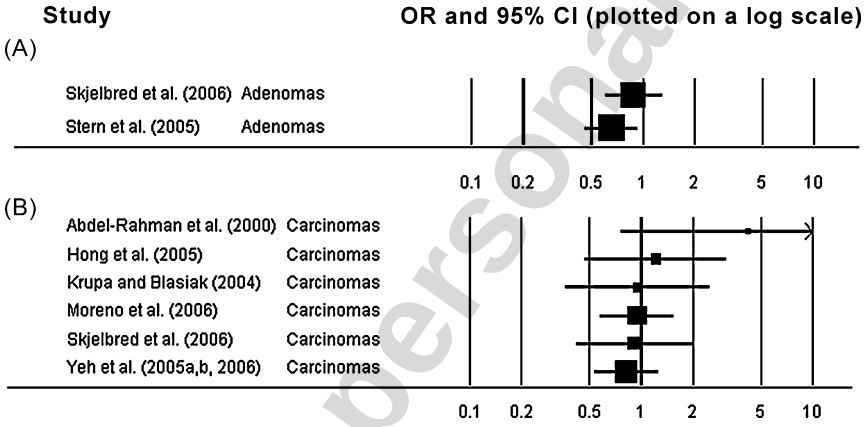

Fig. 3. Odds ratios for the relation between *XRCC1* R399Q polymorphism, adenoma (A) and CRC (B) risk in the reviewed studies. For each study, the odds ratio for the homozygous variant genotype estimated is plotted with a box, and the area of each box is inversely proportional to the variance of the estimated effect. Horizontal lines show 95% confidence interval. Individuals with homozygous wild-type genotype represent a referent group.

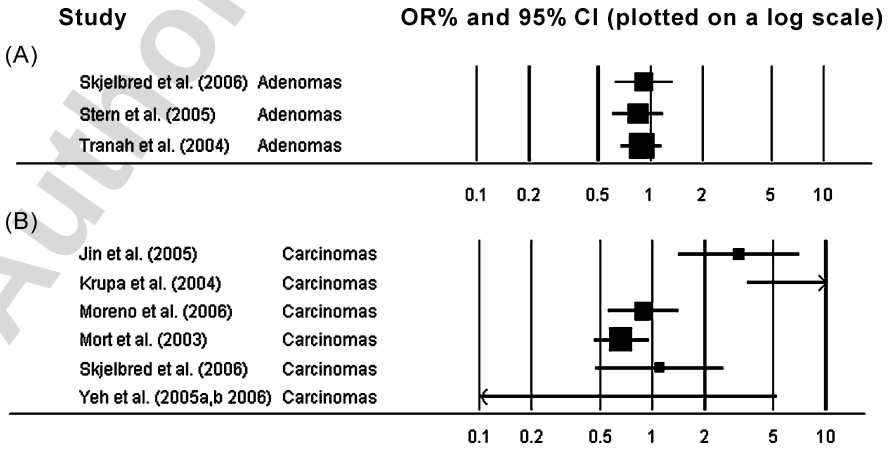

Fig. 4. Odds ratios for the relation between *XRCC3* T241M polymorphism, adenoma (A) and CRC (B) risk in the reviewed studies. For each study, the odds ratio for the homozygous variant genotype estimated is plotted with a box, and the area of each box is inversely proportional to the variance of the estimated effect. Horizontal lines show 95% confidence interval. Individuals with homozygous wild-type genotype represent a referent group.

Taiwan (the same population size and same polymorphisms in both studies). The NER *XPD* K751Q polymorphism did not show any association with CRC. The authors also analyzed this polymorphism in combination with other two of genes involved in different DNA repair pathways. They found that the 751Q allele, when present in individuals with *XRCC1* 399RR and *XRCC3* 241MM genotypes, moderately increased risk of CRC (OR, 2.43; 95% CI 1.21–4.90); particularly among younger individuals and for rectal cancer cases. In a recent study, Yeh et al. combined the results for biotransformation and DNA repair polymorphisms in the same cohort [67]. A combination of risk genotypes for *XPD* K751Q, *CYP1A1*2C* and *GSTT1* have been associated with increased CRC risk in males ($P_{trend} < 0.01$).

Starinsky et al. [68] published a peculiar study on several SNPs in different genes, including *XPD* K751Q, relevant for CRC. They analyzed a heterogeneous population from Israel (456 cases and 87 controls), composed mainly of patients of Ashkenazi origin (64.25%). It is not a true case-control study, since the authors stratified the cases into two subgroups (with follow-up): below and up the arbitrarily chosen age of diagnosis of 50 years. SNPs were tested within candidate genes in association with key phenotypic features in CRC patients. No association was found for the *XPD* polymorphism, except when the analyses were limited to the Ashkenazi subgroup, in which the Q allele was associated with higher age at diagnosis. The above population is known to have particular genetic characteristics.

In the study of Mort et al. [69], several SNPs were analyzed in *XPD*, *XPG*, *XPF* and *ERCC1*. No effect was observed for any of these NER SNPs in a British population of a very limited size (45 cases and 71 controls, not all assayed for all SNPs). The results are presented only as allelic frequencies for cases and controls and not in terms of number of individuals with a specific genotype. Besides, analyzed polymorphisms are not very clearly specified and described (i.e. they are presented only with the exon position, without reference for codon, base-change, etc.). All these aspects make a comparison with the other studies very difficult.

Recent association studies of Skjelbred et al. [70,71] were based on the same population of cases (carcinomas, and diagnosis-based high- and low-risk adenomas) and healthy controls from Norway (for details see Table 2). No significant association with CRC was found for the NER polymorphisms included in each study (*XPD* K751Q and *ERCC1* N118N). However, a significant association between *XPD* 751Q allele and risk of adenomas was reported, but significancy was limited only to the low-risk adenoma group (OR, 1.40; 95% CI, 1.03–1.89) [71]. These limited associations may be ascribed for following reasons. Firstly, the authors hypothesized that this particular *XPD* polymorphism may be of importance for arresting the adenoma–carcinoma sequence in the low-risk phase and facilitate regression of adenomas. The second is that the carcinoma group, as well as the high-risk adenoma group sample size was still too small to draw any conclusion. In the second study, *ERCC1* N118N polymorphism and risk of adenomas and CRC were investigated in the same cohort. No significant association was found. The authors tested the gene-environment interactions between the haplotype of three polymorphisms included (*ERCC1* of NER pathway plus other two SNPs in two genes connected with cell cycle control located on the same chromosome of *ERCC1*), cigarette smoking and alcohol intake. No significant associations were found. According to the authors, the cases and controls were matched by sex, but not by age [70].

The largest study by the number of individuals (772 cases and 777 controls) showed no association for any of the 15 polymorphisms in seven NER genes analysed with colorectal high-risk adenomas [72]. However, after considering smoking status, the three linked nonsynonymous SNPs in *XPC* (R492H, A499V, and K939Q) showed to modulate smoking related risk for adenoma. In particular, *XPC* 492R, 499A, and 939Q alleles were associated with an increased risk. The results are supported by a proper design of the study (large size and matching) and by the selection criteria for patients and controls (controls are without evidence of a polyp or other colon lesions). Although the population consisted of different ethnic groups (among which Caucasians represented a majority), authors included this variable into the statistical analysis.

Bigler et al. [73] evaluated the associations between *XPD* D312N, K751Q and *XPG* D1104H, and risk of colorectal adenomatous or hyperplastic polyps. The study was conducted on a quite large population of patients with different diagnosis (305 with adenomatous polyps, 196 with hyperplastic polyps and 122 with both types of polyps) and 621 polyp-free controls by colonoscopy. Adenomatous polyp risk was significantly increased in individuals with the homozygous variant *XPD*-combined genotypes (i.e. with at least two variant alleles of these polymorphisms; OR, 1.57; 95% CI, 1.04–2.38). Age stratification showed that the *XPD* association was limited to the subjects $\geq$60 years old (OR, 3.77; 95% CI, 1.94–7.35). On the other hand,

individuals carrying *XPG* 1104 HH genotype showed a significantly decreased risk of developing hyperplastic polyps (OR, 0.36; 95% CI, 0.13–0.98). This association was observed predominantly in subjects <60 years old (OR, 0.20; 95% CI, 0.05–0.91). The studied individuals, recruited in the USA, were not specified for the ethnicity (Caucasians, Afro-Americans, etc.), which may inflate the results. Concerning modifiers, heavy smokers with homozygous variant genotype for both *XPD* polymorphisms, or wild type for *XPG*, had a significantly increased risk of adenomatous polyps (OR, 3.93; 95% CI, 1.68–9.21 and OR, 1.59; 95% CI, 1.01–1.25, respectively), compared with non-smokers with wild type genotype. Other interactions, like alcohol, meat consumption or vitamin intake, were not associated with any of the different types of polyps.

The outcomes from association studies on polymorphisms of NER genes do not show any strong and straight association with CRC risk. The most frequently studied, *XPD* K751Q, provided significant associations only with adenomas (Fig. 2). In CRC development the susceptibility may play a more relevant role in the stage of adenomas, which preceeds the onset of cancer.

3.2. Base excision repair (BER)

The BER pathway operates on small lesions such as oxidized or reduced bases, fragmented or nonbulky adducts, or those produced by methylating agents. The single damaged base is removed by base-specific DNA glycosylases (e.g. OGG1). The abasic site is then restored by endonuclease action in a sequence of steps, which includes removal of the sugar residue, DNA synthesis using the other strand as a template, and ligation [58]. Molecules involved in the restoration phase of BER include apurinic/apyrimidinic endonuclease (APE1), polynucleotide kinase, DNA polymerase-β, and XRCC1 [41,58].

The complete list of BER genes/polymorphisms analysed in the association studies is reported in Table 1. Table 3 reviews the 12 studies including one or more polymorphisms of this particular DNA repair pathway. Among 12 BER polymorphisms investigated by Moreno et al. [63], the S326C variant of *OGG1* was the only one associated with an increased risk of CRC (OR, 2.31; 95% CI, 1.05–5.09; $P = 0.031$, for the recessive model combining wild type and heterozygous genotypes). This association was stronger in younger individuals ($P_{interaction} = 0.01$). A significant association was observed for the R allele of *POLB* P242R polymorphism with decreased CRC risk (OR, 0.23; 95% CI, 0.05–0.99; $P = 0.038$). However, the R allele is very rare; there were few individuals with heterozygous and none with homozygous variant genotype. Three *XRCC1* SNPs (R194W, R280H, and R399Q) were evaluated as well, but no significant association was observed. Only for R194W and R280H polymorphisms a significant interaction with age ($P = 0.04$; $P = 0.05$; respectively) was found: the variant allele for both polymorphisms was associated with a decreased CRC risk among individuals ≤54 years, when compared to those aged ≥70 years.

A Korean study [74] evaluated the same three *XRCC1* SNPs in association with CRC risk. Individuals carrying the 399Q allele had a higher risk than those carrying the 399RR genotype (OR, 2.00; 95% CI, 1.15–3.47; $P = 0.047$). A significant association between the combined alleles 194R-280R-399Q and an increased risk for CRC was found (OR, 1.59; 95% CI, 1.01–2.49). Alcohol intake was significantly associated with increased CRC risk (OR, 2.60; 95% CI, 1.46–4.62; $P = 0.001$). In particular, this association was observed in individuals with combined alleles 194W-280R-399R, 194W-280H-399R, and 194R-280R-399Q.

Yeh et al. [65–67] observed no association for *XRCC1* R399Q with CRC risk, except for younger subjects (≤60 years) with the 399RR genotype, compared to those with 399Q allele (OR, 1.46; 95% CI, 1.06–2.99; $P = 0.02$). A slightly increased CRC risk appeared for individuals with the combination of *XRCC1* 399RR, *XRCC3* 241MM and *XPD* 751Q variant allele genotypes. These results are in agreement with a general idea that susceptibility to cancer may be modulated by some particular combinations of "unfavorable" polymorphisms, although the gene–gene interactions are still quite difficult to explain at the current state of our knowledge.

There are six other studies including at least one of the three *XRCC1* polymorphisms (R194W, R280H, and R399Q) [64,69,75–78]. Briefly, the majority of them did not find any association with CRC risk, except for [75,77]. These studies present their major weakness either in the size of individuals genotyped (48 cases and 48 controls, 51 cases and 100 controls, respectively) or in the way the data were evaluated [77].

Skjelbred et al. [71] also evaluated the possible associations of the same three *XRCC1* SNPs with adenoma and CRC risk. The 280H allele was associated with enhanced risk for adenomas (OR, 2.30; 95% CI, 1.19–4.46). A significant protective effect was found for carriers of the *XRCC1* 399 variant allele in the high-risk adenomas (OR, 0.67; 95% CI, 0.46–0.96). Haplotypes in *XRCC1* were tested without a significant outcome. The presence of 399Q allele conferred a reduced risk of

high-risk adenomas (OR, 0.62; 95% CI, 0.41–0.96). This last result is in agreement with findings from Stern et al. [79], who found an inverse association between *XRCC1* 399QQ genotype and adenoma risk in a population of more than 700 cases and 700 controls.

OGG1 is another BER gene very frequently investigated in association studies on CRC. The results on *OGG1* S326C SNP, a part of a large study, were mentioned above [63]. Goodman et al. [64] found a significant trend for the same SNP only in some statistical models, so, in agreement with the author, results should be considered as inconclusive.

Hansen et al. [78] investigated *OGG1* S326C in Norwegian adenoma and CRC patients and healthy controls (see also [70,71]). Carriers of the 326C variant allele had a lowered risk of CRC, whereas no association was found for the risk of adenomas. The same polymorphism in Kim et al. [76] did not show any independent association in a Korean population of 125 colon carcinoma cases and 247 cancer-free controls. However, the meat intake tended to increase OR for colon cancer (OR, 1.72; 95% CI, 1.12–2.76), the tendency being more prominent in CC carriers (OR, 4.31; 95% CI, 1.64–11.48). Similar results were found for smoking (increased OR for smokers carrying CC genotype, 2.75; 95% CI, 1.07–7.53). Kim et al. [80] published a large study (500 sporadic CRC, 124 familial CRC and 524 healthy controls) investigating a rare *OGG1* polymorphism (R154H). This SNP was moderately associated with sporadic CRC (OR, 3.586; 95% CI, 0.98–13.11, $P = 0.053$). Above result raises the possibility that *OGG1* R154H may function as a low/moderate-penetrance modifier for CRC development.

For BER pathway, the majority of studies analyzed variants in *XRCC1*. For *XRCC1* R399Q there is a slight prevalence of studies with an increased CRC risk in association with the variant Q allele, while for adenoma cases the same allele shows a decreased risk (Fig. 3a and b). The CRC studies are focused on different ethnic groups and, unfortunately, positive associations emerge mostly in studies with smaller sample-size. This precludes a clear interpretation of the role of this polymorphism. For two other *XRCC1* SNPs (R194W, R280H) significant associations have been observed only in combinations, suggesting a more relevant role of particular haplotypes rather than single SNPs. The second most frequently analysed SNP, *OGG1* S326C, provided inconclusive outcomes. The variant allele has been described in association with either increased [63,64] or decreased CRC risk [78], and also in no association at all [76]. Several studies analysed interactions between BER SNPs with modifiers (age, gender, smoking habit, alcohol and meat consumption). Overall, age stratification appears to be important: an influence of genetic polymorphisms seems to be more relevant in individuals with younger age at the diagnosis (i.e. below 60 years).

3.3. Double-strand breaks repair (DSB repair)

Double-strand breaks (DSBs) are produced by replication errors and by exogenous agents, such as ionizing radiation. DSBs repair is intrinsically more peculiar since no undamaged template is available [81]. At least two pathways of DSB repair are arbitrarily recognized: the homologous recombination (HR) pathway and the non-homologous end-joining repair (NHEJ) pathway. In the HR, DNA ends are resected, the newly exposed 3′ single-stranded tails then invade the double helix of the homologous, undamaged partner molecule, strands are extended by DNA polymerase, then cross-over yield two intact DNA molecules. This pathway involves more than 16 proteins, including products of the breast cancer genes *BRCA1* and *BRCA2* and *XRCC3*. The NHEJ involves direct ligation of the two DSB ends and also involves numerous molecules [82].

Table 4 presents all studies on one or more polymorphisms of DSB repair genes. Table 1 lists genes/polymorphisms of this pathway. Mort et al. [69] observed a significant over-representation of *XRCC3* 241T allele in CRC patients compared to controls (OR, 1.52; 95% CI, 1.04–2.22). Completely opposite results for the same SNP were found by Jin et al. [83] in a 140 CRC cases and 280 cancer-free controls from China. Carriers of the variant M allele showed a higher CRC risk (OR, 3.13; 95% CI, 1.41–6.95). Similar outcome was reported by Krupa and Blasiak [77] with a surprisingly strong association (OR, 9.45; 95% CI, 8.77–11.65). All other studies did not find any association for this polymorphism [63–67,71,79]. Only one study explored other SNPs in *XRCC3* (4541 A → G, 17893 A → G) on 932 adenoma cases and 1282 controls from the USA [84]. No association between these SNPs and colorectal adenoma was recorded.

Other polymorphisms of DSB genes were included in three studies [63,64,84]. *XRCC2* R188H did not show any significant association with colorectal adenoma risk [84] and with CRC risk [63]. In the latter study, no association was found for *XRCC9* (T297I). The authors indicated that both polymorphisms are rare (especially *XRCC9* polymorphism) and further studies on larger populations are necessary to reach a sufficient statistical power and representation of all genotypes. *NBS1*

E185G is another SNP investigated in DSB genes. No association of above SNP with colon cancer risk was reported on 216 male cases and 255 male controls [64].

In summary, no strong associations emerged for DSB gene polymorphisms from the reviewed studies (Fig. 4a and b). *XRCC3* T241M polymorphism was associated with CRC risk, but with opposite directions, as reported in [69,77,83]. Conflicting data from association studies between polymorphisms and cancer susceptibility are not unusual and often result from insufficient sample size ([69,77] investigated far less than 100 patients). No main interactions of modifiers (i.e. smoking, alcohol, meat consumption, fatty acids and antioxidants intake) emerge with SNPs in DSB repair genes. In the study of Jin et al. [83], the carriers of *XRCC3* 241M allele non-smokers and non-alcohol drinkers, showed an increased CRC risk (adjusted OR 4.85, 95% CI: 1.59–14.76 among non-smokers and adjusted OR 3.72, 95% CI: 1.48–9.39 among non-alcohol drinkers, respectively). In this case, the stratification reduced drastically the number of observations within each group. Yeh et al. [65–67] did not find any association for *XRCC3* T241M, but a stratification of the patients for meat consumption revealed that individuals with 241TT genotype and low consumers of meat had an increased risk of CRC (OR, 2.34; 95% CI, 1.28–4.29, $P_{\text{interaction}} = 0.02$). Particularly enhanced risk was recorded in rectal cancer patients. In [67], the combination of *XRCC3* T241M wild type genotype and *CYP1A1*2C* variant GG genotype was associated with increased CRC risk in women (OR, 3.1, 95% CI, 1.3–7.0, $P < 0.01$). In this case the stratification for dietary/lifestyle risk factors and gender was justified by the large size of the cohort (>700 individuals). The effect of age did not emerge, except for [83], where *XRCC3* 241M allele was associated with CRC risk among older individuals (>60 years).

3.4. Mismatch repair (MMR)

Specific sequence motifs comprised of dinucleotide repeats are known to be unstable in some human cancer. This phenotype of ‘‘microsatellite instability’’ is caused by defects in MMR in HNPCC and in a variety of sporadic cancers. MMR removes nucleotides mispaired by DNA polymerases and insertion/deletion loops that result from slippage during replication of repetitive sequences or during recombination. Defects in this system dramatically increase mutation rates, accelerating the process of oncogenesis [41]. Several genes are involved in MMR, including *hMLH1*, *hMSH2*, *hPMS2*, and *hMSH6* [6].

To our knowledge, there are five studies investigating the role of MMR polymorphisms for sporadic CRC susceptibility (Table 5). Analysed genes/polymorphisms are shown in Table 1.

Berndt et al. [85] investigated four SNPs in three MMR genes in a fairly similar population as in [62]. *hMSH3* 1036A variant allele was associated with an increased CRC risk ($P_{\text{trend}} = 0.02$). After stratification for tumor localization, *hMSH3* 940Q variant allele was associated with an increased risk of proximal colon cancer and *hMSH6* 39E variant allele with an increased risk of rectal cancer ($P_{\text{trend}} = 0.005$ and $P_{\text{trend}} = 0.04$, respectively). Haplotype containing the variant allele at both *hMSH3* loci was associated with an increased risk of proximal colon cancer ($P_{\text{trend}} = 0.04$). Stratification for dietary habits revealed that individuals with haplotype including one copy of both *hMSH3* 1036A and 940Q variant alleles and higher daily processed meat intake (>10.1 g/day) exhibited increased CRC risk ($P_{\text{interaction}} = 0.002$).

In a Korean population of 330 healthy individuals, 107 sporadic CRC patients and 107 of their first-degree relatives, Kim et al. [86] did not find any association of four SNPs (*hMLH1* (I219V, V384D) and *hMSH2* (L390F, gIVS12)) with sporadic CRC risk.

Yu et al. [87] investigated *hMLH1* (−93G → A and I219V) and *hMSH6* (G39E) polymorphisms for association with risk of adenomas. Multivariable-adjusted OR of combined heterozygous and homozygous variant showed no association for the three SNPs in three groups of cases (401 adenoma cases, 195 hyperplastic polyp cases and 123 cases with adenoma and hyperplastic polyps; 624 polyp-free controls). No association was found with any of the possible *hMLH1* haplotypes. The risk of hyperplastic polyps differed significantly between individuals with *hMLH1* −93GG and −93AA + AG genotypes when evaluated in interaction with smoking habit ($P_{\text{interaction}} = 0.02$). The population consisted mainly of Caucasians (97%), an adjustment for ethnicity did not change the outcome.

The study by Starinsky et al. [68] included one MMR SNP (*hMSH2* G322D), but no results are provided.

Exonuclease 1 (EXO1) gene product interacts directly with MMR proteins MSH2, MSH3 and MLH1 in human cells and several mutations at this gene are peculiar of HNPCC patients [88]. Yamamoto et al. [89] have investigated the relationship between two *EXO1* SNPs (T439M, P757L) and the development, progression and metastasis of sporadic CRC. In a Japanese population (102 cases and 110 controls) they have found an association between M allele of *EXO1*

T439M and increased risk of CRC (OR, 2.37, 95% CI, 1.23–4.56, $P = 0.01$). Additionally, patients with *EXO1* 757LL genotype exhibited a reduced risk of CRC by considering PP and PL genotypes as referent (OR. 0.40, 95% CI, 0.18–0.87, $P = 0.02$). Individuals carrying putative risk genotypes for both polymorphisms (TM and MM for *EXO1* T439M and PL for *EXO1* P757L) were at five-fold higher risk of CRC ($P = 0.007$).

Peterlongo et al. [90] evaluated two SNPs in the *hMSH6* gene (−159C → T and V509A) for association with sporadic CRC. No association for any of these SNPs was observed in 167 CRC cases and 190 controls (American–Jewish cohort).

There are still limited data on MMR polymorphisms and CRC risk for drawing any conclusion at present. [85] found significant associations with *hMSH3* SNPs and [87] found a possible modifying effect of smoking for hyperplastic polyp risk in *hMLH1* −93A carriers. Otherwise, the studies did not reveal clear positive associations. Interestingly, polymorphisms in *EXO1* seem to modulate inversely CRC risk, but only one study is available [89] and these results should be confirmed on larger, ethnically homogeneous populations.

3.5. Direct repair

O^6-methylguanine methyltransferase (MGMT) is a ubiquitous repair protein, vital in minimizing the mutagenic effects of alkylating agents, covalently binding at O^6 position of guanine. MGMT acts as a single protein that reverses alkylation damage, catalyzing the transfer of alkyl groups from guanine to an active site of cysteine [91]. MGMT participates in a single reaction only, and is thereby irreversibly inactivated [92].

Four studies have analysed *MGMT* polymorphisms in relation to CRC risk (Table 6). The association between *MGMT* I143V and L84F polymorphisms and risk of CRC was assessed in two American nested case-control studies [93]. The first population consisted of 197 women with CRC and 2,500 cancer-free women, while the second included 271 male CRC cases and 451 cancer-free men as control group. Cases were matched with controls for age and smoking history. A significant inverse association between the *MGMT* 143V allele and CRC risk was found only in women. No association was found for *MGMT* L84F. After the stratification for smoking, alcohol intake, body mass index (BMI), postmenopausal hormone use, folate and meat intake (the last five factors were analysed only in women), an increased CRC risk was found among women carrying the 84F allele and consuming more than a 0.5 alcoholic drink/day ($P_{\text{interaction}} = 0.03$). A BMI $\geq$25 was inversely associated with CRC risk only among women carrying 84P allele ($P_{\text{interaction}} = 0.04$), whereas women with 143V allele and BMI $\geq$25 had a reduced risk of CRC (OR, 0.38; 95% CI, 0.18–0.76). A significant interaction was also found between *MGMT* L84F polymorphism and postmenopausal hormone use ($P_{\text{interaction}} = 0.03$). A previously postulated inverse association between current postmenopausal hormone use and risk of CRC [94] was partially confirmed only among females bearing *MGMT* 84LL genotype (OR, 0.52; 95% CI, 0.34–0.80). In postmenopausal women, *MGMT* 143V allele significantly reduces the risk of CRC and increases the protective effect of postmenopausal hormone use among current users.

No association was found in the other studies on *MGMT* polymorphisms [63,64,73], however, the data available are still relatively scarce, precluding any conclusion.

3.6. Pharmacogenomics and CRC: prognosis and individual susceptibility

The prognosis of a patient with CRC is highly impacted by various factors at the time of diagnosis, such as localization of the tumor, quality of surgical procedures, gender, age, and patient's overall performance status [95]. A significant impact on the development of more efficient/less toxic treatment strategies is represented by proper information on the clinical/pathological staging and the possibility to identify cancer patients with high likelihood of recurrence, or experiencing clinical toxicity. Interindividual variations in response and toxicity to a particular therapy may be due to genetic alterations in drug targets, metabolizing enzymes, efflux and DNA repair systems at the genomic, mRNA and protein levels. Thus, the main aim of pharmacogenetics screening before treatment is, on the base of the patient's genetic information, the identification of individual response to particular chemotherapeutic agents [96,97]. Determination of genetic polymorphisms is becoming important approach to design a personalized therapy and to provide crucial information for drug development. Presently, only a few promising polymorphisms have been identified, or at least tested, for chemotherapy success and toxicity in CRC treatment. The most studied polymorphisms are in the thymidilate synthase (TS) gene, the main target of chemotherapeutic agents such as 5-fluorouracil and capecitabine, widely used in CRC treatment [95]. DNA repair polymorphisms have

also been investigated in relation to platinum agents, cisplatin and oxaliplatin, since DNA repair capacity modulates the chemoresistance to platinum-based compounds [96]. Particularly enzymes of NER pathway repair DNA damage caused by platinum agents and several studies demonstrated the inverse relationship between impaired DNA-repair capacity and increased response rates to platinum drugs [98].

Three studies addressed the possible modulating role of different DNA repair polymorphisms in relation to the response to 5-fluorouracil/oxaliplatin treatments. In 73 patients with metastatic CRC three common *XPD* polymorphisms (C156A, D312N, and K751Q) were investigated for their possible impact on the outcome of the therapy [99]. Concerning *XPD* K751Q, 5 out of 21 (24%) patients with the 751KK genotype responded, versus 4 out of 39 (10%) with 751KQ, and 1 out of 10 (10%) with the 751QQ genotypes ($P = 0.015$). The median survival in months for individuals with the 751KK genotype was 17.4 (95% CI 7.9–26.5) versus 12.8 (95% CI 8.5–25.9) for those with 751KQ and 3.3 (95% CI 1.4–6.5) with 751QQ ($P = 0.002$). The other two *XPD* polymorphisms were neither associated with any response to 5-fluorouracil/oxaliplatin nor with survival. Stoehlmacher et al. [100] observed an increased risk of chemotherapy failure in individuals with at least 1 Gln variant allele in *XRCC1* R399Q (as assayed for in 61 patients with the same therapy as above). The role of two *ERCC1* polymorphisms (codon 118 and 3′-untranslated region) was recently evaluated for the clinical outcome to platinum-based chemotherapy in 106 patients with advanced refractory CRC [101]. SNP in codon 118 causes a C → T substitution, but codes for the same amino acid, asparagine, and may be associated with differential gene expression, whereas SNP in 3′-untranslated region may affect mRNA stability. The authors found a significant association between the *ERCC1* codon 118 polymorphism and the clinical outcome: patients with the C/C genotype had a median survival of 15.3 months (95% CI, 6.0–12.1) versus 11.1 months (95% CI, 5.8–16.2) of those with C/T and T/T genotypes. Viguier et al. [102] analyzed 91 patients treated for metastatic CRC in a retrospective study. They observed a higher response to combined chemotherapy of oxaliplatin/5-fluorouracil in individuals with variant T allele in *ERCC1* codon 118 polymorphism, no significant differences were detected when patients were treated only with 5-FU or with 5-FU and irinotecan. High *ERCC1* gene expression levels were shown to be associated with shorter surviving period in CRC patients treated with 5-FU/oxaliplatin [103]. By the use of univariate analysis, adjusted for age, sex, and Duke's stage, *ERCC1* 19007T > C was associated with worse prognosis of CRC (hazard ratio-HR, 1.51; 95% CI, 1.01–2.27), while *XRCC1* R399Q (HR, 0.38; 95% CI, 0.17–0.85), *XRCC3* T141M (HR, 0.66; 95% CI, 0.45–0.97), and *MGMT* L84F (HR, 0.14; 95% CI, 0.02–0.99) were associated with better prognosis, particularly in patients with adjuvant chemotherapy [63]. Gordon et al. [104] investigated 21 polymorphisms in 18 genes (cell-cycle regulation, drug metabolism, tumor microenvironment and DNA repair) for the risk of CRC recurrence in 90 patients treated with 5-FU combined with radiotherapy. SNPs in DNA repair genes (*ERCC1*, *XRCC3*, *APE1* and *RAD51*) did not modulate the risk of CRC recurrence.

Despite scarce information, there is growing evidence that the ultimate goal of therapy should be the use of anticancer drugs that comply with the genetic profile of the patients, in order to maximize potential response to therapy [96].

4. Discussion

Growing evidence suggests that genetic predisposition to cancer acts via a combination of high-risk variants in a set of low- and medium-penetrance genes, rather than via a few high-penetrance genes [105]. This applies for sporadic CRC in particular, where a combination of low-penetrance susceptibility alleles and multiple environmental factors seems to be of relevance [6]. The role of genetic variants (e.g. SNPs) in genes encoding key players in the susceptibility to the sporadic CRC is not satisfactorily clarified at present. One of the key players in CRC risk seems to be *MTHFR* C677T [23], along with polymorphisms in genes involved in cell-cycle and inflammatory processes. Recent years have also evidenced a growing attention devoted to the role of DNA repair genes as CRC risk modulators. Interindividual variations in DNA repair genes may confer altered DNA repair capacity, and thus an enhanced cancer risk [45].

In this review, we summarized the state of the art for DNA repair genetic polymorphisms in association with colorectal adenoma and CRC risk. Although the present review encompasses more than 20 studies on the above topic, the results remain inconclusive. The number of investigated genes and related polymorphisms is extensive (29 and 71, respectively), but only few of them were analysed in two and more studies. In the majority of cases, we could only report the study-specific outcomes, while a comparison of results to highlight general trends was not feasible. In general, there are no strong associations between DNA repair

SNPs and adenoma or CRC risk, observed repeatedly in more investigations. Many studies did not reveal any significant association at all. The majority of studies focused on polymorphisms in BER and in NER pathways, *XRCC1* and *XPD* in particular. Two recent large studies, comprising 980 cases and 1200 controls, reported a decreased risk for adenomas in association with *XRCC1* R399Q variant allele [71,79], whereas in considerably smaller populations CRC risk was moderately increased in association with this variant allele [74,75]. Variant allele in *XPD* K751Q was associated with increased adenoma, but not CRC, risk [71,73]. Discrepancies between premalignant adenoma and CRC are difficult to explain, but adenoma risk was studied on a significantly larger and better characterized populations. This interesting aspect certainly deserves proper attention in future studies.

Although there is a weak association between single DNA repair polymorphisms, when assayed for adenoma and CRC risk, more realistic information may be provided by analyzing polymorphisms in combinations. Single SNPs in low-penetrance genes are unlikely to affect significantly the susceptibility to cancer, but an ''adverse combination'' of less favorable genetic variants can exert and amplify a negative effect. However, analysis of SNPs in combination reduces the number of observations and decreases the statistical power of the studies. Only a few studies addressed DNA repair gene–gene interactions so far: particular combinations of *XPD* K751Q, *XRCC1* R399Q and *XRCC3* T241M wild type genotypes were associated with an increased CRC risk in a cohort of 727 CRC patients and 736 controls from Taiwan [66]. Investigations of more SNPs in the same DNA repair gene (especially for *XPD, ERCC1*, *EXO1*, and *MGMT*) are shown in Tables 2–6. In this context, haplotype studies appear as more informative. A haplotype, a set of closely linked alleles (SNPs), is inherited as a unit, ultimately covering the variability within a gene [106]. Modulating effect of haplotypes was investigated three-times for *XRCC1* combined polymorphisms (R194W, R280H and R399Q). Specific *XRCC1* haplotypes increased the risk of CRC in interaction with alcohol intake [74], and adenoma risk in concomitance with fatty acid intake [79]. The same haplotype was associated with a decreased CRC risk in young individuals only [63].

The investigation of gene-environment interactions implies the simultaneous study of both environmental exposure and relevant genetic polymorphisms. While for genotyping the methods are quite accurate, a reliable determination of the environmental exposure is both laborious and expensive (i.e. measurement of external/internal dose of a chemical or its metabolites) or unreliable and non-quantitative (i.e. information based on questionnaires only), often missing the target tissue. Even more difficult is the characterization of individuals for simultaneous exposures to different factors (i.e. occupational exposure and lifestyle habits in different combinations), with subsequent conversion into reliable data for statistics [15]. However, it is likely that some of the candidate low-penetrance genes may contribute to CRC only in concomitance with certain dietary and/or lifestyle factors. In the present review, several studies included stratification for main modifying factors (e.g. smoking, alcohol consumption, gender and age), while considerably fewer studies included an analysis for dietary habits (meat, vitamin, vegetable/folate intake, etc.). Interactions between DNA repair SNPs, smoking, alcohol and specific dietary intake were found sporadically. The same situation can be observed for gender. Several studies do not find any differences between males and females while in [93,67] the main associations between CRC risk and SNPs were reported in women only. A number of studies detected a different susceptibility according to age. Interestingly, significant associations of particular SNPs and adenoma or CRC risk seem to be evident more frequently in younger individuals (<50–60 years) [63,65,66,73,75]. However, we noticed a considerable variety in the design of the reviewed studies, particularly concerning studied populations. A possible comparison of results, as well as drawing any firm conclusion, is seriously hampered by differences/inconsistencies in following points: size of controls and cases, combining different ethnic groups, improper or absent matching cases and controls for sex and age, lack of information on CRC localization and staging and inconsistent selection and recruitment of the control group.

Critical analysis of the reported association studies revealed following limitations. The most important critical point is associated with the often too small size of cohorts of cases and controls, resulting in a low statistical power and false, by chance, positive or negative outcomes. Several studies are showing the bias introduced by analyses performed in small populations [17]. In this context, the number of studies exceeding 500 cases was currently still limited, both for colorectal adenoma and CRC (6 and 2, respectively). An additional important aspect concerns the inclusion (often disproportional) of different ethnic groups into the cases and the controls, with subsequent obscuring of the outcomes. Different results may be expected due to intrinsic differences in genetic background among Caucasians, Asians, Afro-Americans and other ethnic

groups. Only in the recent DNA repair association studies the statistical analyses the stratification for ethnicity were included [62,64,72,79,83,85].

The proper recruitment of cases and controls represents another key factor, which characterizes different studies. Whereas in adenoma and CRC patients we can follow the use of standard criteria for the diagnosis (e.g. colonoscopy, histological examination), a very complicated situation appears in recruited control individuals. The use of population-based unscreened control group does not prevent inclusion of individuals with undetected polyps, with subsequent attenuation of study findings. The studies including only colonoscopically negative individuals may not be representative of the general population. They rather comprise individuals with any clear indication for colonoscopy, such as putative positive family history or any gastrointestinal problems. On the other hand, the major advantage of this clinic-based approach is obtaining the control group free of polyps or CRC. Another approach is the recruitment of only cancer-free individuals as a control population (i.e. individuals declaring no history of cancer in the past for them and for family, and/or individuals tested for cancer). Since it employs directed questionnaires, the reliability of answers should be considered. Besides, various cancer tests (expensive and laborious) are not yet completely reliable. Optimally, the use of two independent control groups (one screened for colonoscopy and one constituted by healthy general population) would minimize biases.

Proper matching cases and controls for age and sex was also seldomly recorded. Modulating effects of age and sex on CRC onset may only be investigated by comparing matched cohorts. Large-scale whole-genome association studies may also help in a future to implement the quality of the outcomes by searching those SNPs, which exert a real modulating effect on CRC risk. As an example, a scan of 1467 non-synonymous SNPs (for genes of many different pathways) was performed on 2575 CRC cases and 2707 controls from Great Britain [107]. The final outcome is that after correction for multiple testing one SNP only, in a gene involved in receptor binding and signal transduction, remained significant (*AKAP9* M463I). Without any conservative analysis, 44 SNPs, among which few involved in DNA repair, showed a significancy of 5%. However, DNA repair SNPs, reviewed by us, do not seem to exert any modulating role in CRC risk [107]. Such approaches, supported by proper design of the study and by robust statistical analyses, are very promising, and should allow to restrict the analyses to few relevant SNPs and to find out replicable genotype-disease associations. Epidemiological studies, investigating the possible associations between common DNA repair SNPs and risk of CRC, can provide a useful insight into the relationship between cancer and individual susceptibility in response to DNA damage. These studies represent an empirical identification of associations indicating that SNPs in candidate genes may have an impact on a disease, independently of metabolic and other regulatory systems as well as of other genetic and environmental variability [57]. The current challenge is represented by the proof of the biological plausibility for the majority of SNPs, since the phenotypic effects and functional reflections in the majority of cases are not known [60].

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