BEATRIZ REGINA LIMA DE AGUIAR

POLIMORFISMO DE NUCLEOTÍDEO ÚNICO NA PREDIÇÃO DE RADIODERMATITE EM PACIENTES COM CÂNCER DE MAMA: REVISÃO SISTEMÁTICA E META-ANÁLISE

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PROGRAMA DE PÓS-GRADUAÇÃO EM CIÊNCIAS DA SAÚDE

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Dissertação apresentada como requisito parcial para a obtenção do Título de Mestre em Ciências da Saúde pelo Programa de Pós-Graduação em Ciências da Saúde da Universidade de Brasília.

Orientadora: Drª Paula Elaine Diniz dos Reis

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BANCA EXAMINADORA

Profª Drª Paula Elaine Diniz dos Reis (presidente)

Universidade de Brasília

Drª Daniele Xavier Assad

Hospital Sírio Libanês – Distrito Federal

Profª Drª Juliana Forte Mazzeu de Araújo

Universidade de Brasília

Profª Drª Eliete Neves da Silva Guerra (Suplente)

Universidade de Brasília

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Isaac Newton costumava dizer que “Se pude ver além dos demais, foi porque me pus de pé nos ombros de gigantes”. E assim como ele, tive a oportunidade de conhecer vários “gigantes” que contribuíram com cada conquista. Primeiramente, gostaria de agradecer a dois “gigantes”, meus pais Maria do Socorro F. de Lima e João J. de Aguiar, por terem me dado a vida e por lutarem para me permitir ser quem eu sou. Por todo esforço e incentivo diário para que eu possa me dedicar integralmente aos estudos e alcançar meus objetivos. É para vocês que dedico este trabalho. À minha querida irmã, Bárbara Lima de Aguiar, que é uma grande amiga e sempre esteve ao meu lado nestes anos. Digo para você que nunca desista daquilo que você acredita e do que deseja conquistar. Segurarei sua mão sempre que precisar e espero que esse pedacinho da minha história possa lhe mostrar que podemos chegar onde nós quisermos.

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Os genes formam as malhas da rede.

O que tem contato com essa rede e se mantêm retido nela

é o que transforma cada rede individual em um ser.

(Adaptado de O gene: Uma história íntima – Siddhartha Mukherjee)

RESUMO

Introdução: A radiodermatite aguda é uma reação adversa à radioterapia muito frequente em pacientes com câncer de mama, que afeta a qualidade de vida, a estética e a imagem corporal, além de interromper o tratamento em casos de reação severa. A Radiogenômica estuda o potencial de Polimorfismos de Nucleotídeo Único, do inglês *Single Nucleotide Polymorphisms* (SNPs), predizer radiossensibilidade. **Objetivo**: Avaliar o potencial de SNPs predizerem o desenvolvimento ou severidade de radiodermatite aguda em pacientes com câncer de mama que reealizaram radioterapia. **Método**: Trata-se de uma revisão sistemática, de acordo com o *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA 2020). A busca foi realizada na bases de dados CINAHL, Cochrane CENTRAL, EMBASE, LILACS, PubMed, Scopus, e Web of Science. Adicionalmente foi feita busca na literatura cinzenta (Google Scholar, OpenGrey e PROQUEST Thesis & Dissertations) e busca manual na lista de referências dos artigos incluídos. A ferramenta *Critical Appraisal Checklist for Cohort Studies* do *Joanna Briggs Institute* foi utilizada para avaliar risco de viés dos estudos individuais. A metanálise de prevalência dos SNPs em pacientes com câncer de mama que apresentaram radiodermatite foi realizada no *MetaXL® 5.3 software*. A metanálise de associação entre SNPs e severidade de radiodermatite foi realizada usando o *Cochrane Collaboration's Review Manager® 5.4 software (RevMan 5.4).* A certeza da evidência foi avaliada usando a ferramenta *Grading of Recommendation, Assessment, Development, and Evaluation* (GRADE). **Resultados**: Dezesseis estudos tipo coorte atenderam aos critérios de elegibilidade e foram incluídos nesta revisão. Treze estudos apresentaram baixo risco de viés, e três apresentaram risco moderado. Vinte e dois SNPs foram incluídos na metanálise de prevalência. Os dois SNPs mais prevalentes nos pacientes com câncer de mama que apresentaram radiodermatite foram o rs1800469 no gene *TGFβ1* (41%) e o rs3957356 no gene *GSTA1* (36%) ($I^2 \geq 92\%$; $p = 0$). A metanálise de associação de 21 SNPs mostrou que sete genótipos têm associação com radiodermatite grave e cinco genótipos têm associação com radiodermatite leve. No entanto, destaca-se que o genótipo CT do polimorfismo rs3957356 no gene *GSTA1* e o genótipo GG do

polimorfismo rs2282367 no gene *MAT1A* apresentaram baixa certeza da evidência. Todos os outros genótipos apresentaram uma certeza da evidência muito baixa. **Conclusão**: Dados significativos mostram que a genotipagem pode ser uma estratégia para predizer radiodermatite em pacientes com câncer de mama. Sugere-se que estudos de alto rigor metodológico para avaliação de SNPs que foram mais prevalente e que demonstraram uma primeira possibilidade de associação com radiodermatite sejam realizados para confirmar essa hipótese. Além disso, estudos com populações de diferentes etnias e localizações geográficas são necessários para avaliar os SNPs em várias populações.

Palavras-chave: Radiodermatite; Radioterapia; Marcadores Genéticos; Neoplasias da Mama; Revisão Sistemática; Metanálise.

ABSTRACT

Introduction: Acute radiation dermatitis is a very common adverse reaction to radiotherapy in patients with breast cancer, which affects the quality of life, aesthetics, and body image, in addition to interrupting treatment in cases of a severe reaction. Radiogenomics studies the potential of Single Nucleotide Polymorphisms (SNPs) to predict radiosensitivity. **Objective**: To evaluate the potential of SNPs to predict the development or the severity of acute radiation dermatitis in breast cancer patients undergoing radiotherapy. **Method**: This is a systematic review following the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA 2020), published in 2020. The search was performed in CINAHL, Cochrane CENTRAL, EMBASE, LILACS, PubMed, Scopus, and Web of Science databases. Additionally, a search was made in the gray literature (Google Scholar, OpenGrey, and PROQUEST Thesis & Dissertations) and a manual search in the reference list of the articles included. The Critical Appraisal Checklist for Cohort Studies tool of the Joanna Briggs Institute was used to assess the risk of bias for individual studies. Meta-analysis of the prevalence of SNPs in breast cancer patients who had radiation dermatitis was performed in MetaXL® 5.3 software. Meta-analysis of the association between SNPs and radiation dermatitis severity was performed using Cochrane Collaboration's Review Manager® 5.4 software (RevMan 5.4). The certainty of the evidence was assessed using the Grading of Recommendation, Assessment, Development, and Evaluation tool. **Results**: Sixteen cohorts met the eligibility criteria and were included in this review. Thirteen studies had a low risk of bias, and three had a moderate risk of bias. Twenty-two SNPs were included in the prevalence meta-analysis. The two most prevalent single nucleotide polymorphisms in breast cancer that present radiation dermatitis were rs1800469 in the *TGFβ1* gene (41%), and rs3957356 in the *GSTA1* gene (36%) ($I^2 \geq 92\%$; $p = 0$). The association meta-analysis of 21 SNPs showed that seven genotypes are associated with severe radiation dermatitis and five genotypes are associated with lower radiation dermatitis. However, the only ones that showed low certainty of evidence were the CT genotype of the rs3957356 polymorphism in the *GSTA1* gene and the GG genotype of the rs2282367 polymorphism in the *MAT1A* gene. All other genotypes have very low evidence certainty. **Conclusion**: Significant

data show that genotyping of SNPs may be a strategy for predicting radiation dermatitis in breast cancer patients. It is suggested that studies of high methodological rigor to evaluate SNPs that presented high prevalend and that demonstrated a first possibility of association with radiation dermatitis be performed to confirm this hypothesis. Furthermore, studies with populations of different ethnicities and geographic locations are needed to assess SNPs in various populations.

Keywords: Radiodermatitis; Radiotherapy; Genetic Markers; Breast Neoplasms; Systematic review; Meta-analysis.

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ARTIGO

LISTA DE ABREVIATURAS E SIGLAS

A	Adenina
ALAD	*aminolevulinate dehydratase*
APE1	*acclimation of photosynthesis to environment*
ASO	Allele Specific Oligonucleotide;
ATM	*ATM serine/threonine kinase*
BAX	*BCL2 associated X, apoptosis regulator*
BED	Biologically Effective Radiotherapy Dose
BMI	Body Mass Index
BRCA1	*BRCA1 DNA repair associated*
BRCA2	*BRCA2 DNA repair associated*
C	Citosina
CAT	*catalase*
CD44	*CD44 molecule*
CHEK1	*checkpoint kinase 1*
CI	Confidence Interval
COMT	*catechol-O-methyltransferase*
CTCAE	Common Terminology Criteria for Adverse Effects
CTCAE	Common Toxicity Criteria for Adverse Events
DNA	desoxyribonucleic acid
eNOS	*endothelial nitric oxide synthase*
ERCC2	*ERCC excision repair 2, TFIIH core complex helicase subunit*
G	Guanina
GRADE	Grading of Recommendation, Assessment, Development, and Evaluation
GSTA1	*glutathione S-transferase alpha 1*
GSTM1	*glutathione S-transferase mu 1*
GSTP1	*glutathione S-transferase pi 1*
GSTT1	*: glutathione S-transferase theta 1*
Gy	Gray
H2AX	*H2A.X variant histone*

HER2	*glutamyl-tRNA(Gln) amidotransferase subunit HER2*
HR	Hazard Ratio
HWE	Hardy-Weinberg Equilibrium
LCP2	*lymphocyte cytosolic protein 2*
LIG3	*DNA ligase 3*
LIONCO	Laboratório Interdisciplinar de Pesquisa Aplicada à Prática Clínica em Oncologia
LTHA4	*leukotriene A-4 hydrolase*
M	Mitose
MAD2L2	*mitotic arrest deficient 2 like 2*
MALDI-TOF	matrix-assisted laser desorption/ionization time-offlight
MAP3K7	*mitogen-activated protein kinase kinase kinase 7*
MAT1A	*methionine adenosyltransferase 1ª*
MGMT	*O-6-methylguanine-DNA methyltransferase*
MLH1	*mutL homolog 1*
MnSOD	*manganese superoxide dismutase*
MPO	*myeloperoxidase*
MSH2	*mutS homolog 2*
MSH3	*mutS homolog 3*
NBS1	*nijmegen breakage syndrome 1*
NCI	National Cancer Institute
NDUFB6	*NADH:ubiquinone oxidoreductase subunit B6*
NEIL3	*nei like DNA glycosylase 3*
NFE2L2	*nuclear factor, erythroid 2 like 2*
NI	No informed
NOS3	*nitric oxide synthase 3*
OGG1	*8-oxoguanine DNA glycosylase*
ONS	Oncology Nursing Society
OR	Odds Ratio
P21	*p21 protein regulates cell cycle*
PCR	Polymerase Chain Reaction
PCR-RFLP	Polymerase Chain Reaction – Restriction Fragment Length Polymorphism

PECOS acronym	Population, Exposition, Control, Outcomes, Studies acronym
PHLDA3	*pleckstrin homology like domain family A member 3*
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-analyses
PTEN	*Phosphatase and tnsin homolog*
PTTG1	*PTTG1 regulator of sister chromatid separation, securin*
RAD17	*RAD17 checkpoint clamp loader component*
RAD51C	*: RAD51 paralog C*
RAD9A	*RAD9 checkpoint clamp component A*
RD	Radiation Dermatitis / Radiodermatite
REV3L	*REV3 like, DNA directed polymerase zeta catalytic subunit*
RPS6KB2	*ribosomal protein S6 kinase B2*
RT	Radiotherapy
RT	Radiotherapy
RTOG	Radiation Therapy Oncology Group
RTOG	Radiation Therapy Oncology Group
SBRT	Sociedade Brasileira de Radioterapia
SH3GL1	*SH3 domain containing GRB2 like 1, endophilin A2*
SNPs	Single Nucleotide Polymorphisms
SOD2	*superoxide dismutase 2*
SoF	Summary of Finding
T	Timina
TGFβ3	*transforming growth factor beta 3*
TGFβR3	*transforming growth factor beta receptor 3*
TGFβ1	*transforming growth factor beta 1*
TNF-α	*Tumor necrosis factor α*
TP53	*tumor protein p53*
VDR	*vitamin D receptor*
XPD	*Xeroderma pigmentosum D*
XRCC1	*X-ray repair cross complementing 1*
XRCC2	*X-ray repair cross complementing 2*

XRCC3	*X-ray repair cross complementing 3*
ZNF830	*zinc finger protein 830*

SUMÁRIO

1 INTRODUÇÃO

O câncer de mama é o mais frequente em mulheres no Brasil e no mundo, com estimativas aproximadas de 66,3 mil e 2,3 milhões de novos casos, respectivamente, em 2020 (1,2). O tratamento, geralmente, é realizado com combinação das diferentes estratégias terapêuticas sistêmicas e loco-regionais, tais como quimioterapia, hormonioterapia, imunoterapia, cirurgia e radioterapia (3).

A radioterapia é a modalidade terapêutica utilizada em 50% dos planejamentos terapêuticos para o câncer de mama e se baseia na utilização de radiação ionizante para controle do crescimento e da multiplicação de células de rápida proliferação (4,5). Apesar de ser uma terapia local e direcionada para o tecido tumoral, tecidos adjacentes ao tumor que tem alta capacidade proliferativa, como a pele, também são atingidos e sofrem efeitos adversos.

A radiodermatite aguda é uma reação adversa na pele, decorrente da exposição subsequente às doses de radiação ionizante, que ocorre em cerca de 95% dos pacientes com câncer de mama qe realizaram radioterapia (6-8). A lesão na pele da área irradiada se inicia com eritema e, à medida em que as células basais da epiderme vão perdendo a capacidade proliferativa, podem evoluir para descamação seca, descamação úmida, hemorragia, necrose e ulceração (6,9,10). Essa reação tem grande impacto na qualidade de vida, estética e imagem corporal e pode levar à interrupção do tratamento (7,10-12).

Apesar de vários estudos testarem diferentes produtos tópicos e sistêmicos para prevenir ou tratar radiodermatite aguda, ainda não há um consenso na literatura que possibilite fortes recomendações (13,14). Alguns fatores de risco para o desenvolvimento de radiodermatite na mama incluem volume mamário, dose de radiação ionizante, obesidade, estilo de vida, entre outros (6,9,15). Estudos de radiogenômica têm buscado investigar se modificações genéticas, mais comumente polimorfismos de nucleotídeo único (SNP), poderiam influenciar na suscetibilidade ao desenvolvimento de radiodermatite aguda (5).

Este trabalho busca avaliar as evidências da literatura sobre o potencial de modificações genéticas, especificamente SNP, predizer o desenvolvimento de radiodermatite aguda e estarem associadas a graus severos dessa reação.

2 REVISÃO BIBLIOGRÁFICA

2.1. CÂNCER DE MAMA

O câncer é um grave problema de saúde pública e a frequência e mortalidade têm crescido, em decorrência do crescimento e envelhecimento populacional e maior exposição aos fatores de risco (1,2).

O câncer de mama é um conjunto de doenças que iniciam pela divisão e multiplicação descontroladas de células do tecido mamário que surge mais comumente nos lóbulos ou nos ductos (terminal e coletor) mamários (3,16).

2.1.1. Epidemiologia

O câncer de mama é a neoplasia mais frequente em mulheres no mundo, tirando os casos de câncer de pele não melanoma. Em 2020, a incidência no sexo feminino foi de 2.261.419, correspondendo a 11,7% de todos os tipos de câncer e a 24,5% de todos os casos de câncer no sexo feminino (2). Apesar da mortalidade variar de acordo com o subtipo de câncer de mama, a taxa de mortalidade geral em mulheres, em 2020, foi de 6,9% (2). Estima-se que em 2030 a incidência de câncer de mama no mundo seja de 75.900 casos com aumento para 125 mil novos casos em 2040 (2). As estimativas do Globocan (2020) (2) não trazem dados sobre câncer de mama no sexo masculino.

No Brasil, estima-se que ocorram 66.280 novos casos de câncer de mama no sexo feminino em cada ano do triênio 2020-2022, sendo que a região sudeste e sul são as que possuem o maior risco estimado de casos de câncer de mama no sexo feminino (1). Isso pode estar relacionado com o acesso aos serviços de saúde para diagnóstico. Em 2019, foram registrados 18.068 óbitos por câncer de mama no sexo feminino e 227 óbitos por câncer de mama no sexo masculino no Brasil (17).

A prevalência e a mortalidade do câncer de mama variam de acordo com o índice socioeconômico dos diferentes países e regiões (3). Em parte, isso reflete a maior exposição a fatores de risco, em determinadas regiões, e o acesso à medidas de rastreamento e diagnóstico do câncer de mama (3). Quando diagnosticado em estágios iniciais, aproximadamente 70-80% dos casos são curáveis (3).

2.1.2. Fatores de Risco

Os principais fatores de risco para câncer de mama incluem:

Tabela 1 – Fatores de risco para câncer de mama (1-3,16,18,19)**.**

Fatores Intrínsecos	Idade > 50 anos Grande volume mamário História lesões mamárias (alterações fibrocísticas, fibroadenoma, hiperplasia ductal típica, hiperplasia lobular atípica) Diabetes tipo 2
Hábitos de vida/ comportamentais e ambientais	Tabagismo Etilismo Obesidade Dieta rica em gordura Sedentarismo Exposição à radiação ionizante
Fatores Genéticos	Histórico familiar de câncer de mama/ovário Mutação dos genes *BRCA1 e BRCA2* Síndrome Li-Fraumeni (mutação em*TP53*) Síndrome de Cowden (mutação em *PTEN*)
História Reprodutiva e Fatores Endócrinos	Menarca precoce e Menopausa tardia Exposição a estrógenos Terapia de reposição hormonal Baixa paridade Idade avançada no primeiro parto Não amamentar

2.1.3. Triagem, Diagnóstico e Subtipos

A mamografia é uma estratégia de rastreamento para detecção do câncer de mama em estágios iniciais e comumente feita em mulheres com idade entre 50 a 59 anos (2,3). O rastreamento por ultrassonografia pode ser realizado em mulheres com mama densa e o rastreamento por ressonância magnética pode ser realizado em mulheres que realizaram análise genética e identificaram que tem risco elevado de desenvolver câncer de mama (19). O diagnóstico é feito com base no resultado de biópsia (3).

O estágio do câncer de mama pode ser classificado em *in situ* ou invasivo. O câncer de mama *in situ* se refere a proliferação desordenada de células tumorais que permanecem confinadas à membrana basal da camada de células de origem (16). O câncer de mama invasivo se refere a proliferação de células tumorais que ultrapassa a membrana basal da camada de células de origem e cresce no tecido mamário circundante (16).

O câncer de mama é extremamente heterogêneo e, por isso, dizemos que se trata de um grupo de doenças (19). Hoje, a *American Cancer Society* (16) estima que existam cerca de 21 subtipos histológicos de câncer de mama e o mais comum em mama feminina é o carcinoma de células epiteliais *in situ* e invasoras (1). Eles podem ser divididos ainda, quanto ao padrão molecular, em cânceres positivos ou negativos para fatores hormonais (estrógeno e progesterona) e positivos ou negativos para o marcador *HER2* (16,19). O subtipo de câncer que é negativo tanto para fatores hormonais quanto para o marcador *HER2* é chamado de câncer de mama triplo negativo (3).

A extensão local do câncer de mama e a disseminação em tecidos vizinhos determinarão o estadiamento, que será fundamental, juntamente com os testes moleculares, para o planejamento do tratamento (16). Para o câncer de mama avançado, com doença metastática, as terapias disponíveis não promovem cura, mas podem ajudar a melhorar a expectativa de vida associada à melhora da qualidade de vida (3).

2.1.4. Tratamento

O tratamento do câncer de mama pode ser local (por cirurgia e radioterapia) ou sistêmico (com uso de quimioterapia, hormonioterapia e imunoterapia) (3). Geralmente é feita uma combinação de técnicas de acordo com o subtipo do tumor, marcadores moleculares, estadiamento e características individuais do paciente (16).

Discutindo melhor sobre as terapias loco-regionais, a cirurgia de mama é feita com o objetivo de remover todo o tumor e as margens livres. Pode ser feita mastectomia ou cirurgia conservadora da mama a depender do subtipo tumoral, da extensão da doença, do estadiamento, dos exames de imagem e das características clínicas das pacientes. Mastectomia bilateral pode ser realizada em casos que há grande chance de um segundo tumor de mama se a paciente é *BRCA1/BRCA2* positivo (16,20). A cirurgia conservadora da mama é geralmente seguida por radioterapia (16,20).

A radioterapia para o câncer de mama pode ser feita na própria mama, na parede torácica, na região supra e infraclavicular e/ou na axila (16,21). Pode, ainda, ser realizada antes ou após outras terapias principais (15). Quando realizada antes da terapia principal, tem como objetivo reduzir o tamanho e o volume da massa tumoral (15,20). Quando realizada depois do tratamento principal, tem como objetivo destruir qualquer célula tumoral e micrometástases que tenham restado localmente (15,20). Os princípios da radioterapia serão mais bem detalhados a seguir.

2.2. RADIOTERAPIA

A radioterapia é uma modalidade terapêutica local para o câncer que utiliza feixes de radiação ionizante para inibir ou controlar o crescimento de células tumorais, podendo ser usada de forma isolada ou em conjunto com outras terapias (4). É utilizada em cerca de 50-60% dos tratamentos para o câncer com finalidade curativa e paliativa (4,5,22).

Existem duas modalidades de radioterapia. A braquiterapia utiliza uma fonte de radiação ionizante que fica em contato com o tecido tumoral e permite que doses maiores de radiação atinjam o tecido alvo (23,24). No entanto, é muito raro utilizar braquiterapia no tratamento de câncer mama. A Teleterapia, também chamada de radioterapia externa, é o tipo de radioterapia mais comum e realizada com uso de máquinas, mais comumente aceleradores lineares, que permitem que a fonte de radiação ionizante fique posicionada a uma certa distância do paciente e são programados para incidir no tumor (23,24). Ambas as técnicas são utilizadas no tratamento do câncer de mama.

2.2.1. Mecanismo de Ação da Radioterapia

Para que uma célula normal consiga se multiplicar, o ciclo celular dura cerca de 10 a 20 horas (25). Células tumorais tendem a proliferar mais rapidamente. Durante as fases G2 e Mitose (M) do ciclo celular a cromatina está mais compactada e dificulta a ação de enzimas de reparo, aumentando a probabilidade de ocorrer danos ao DNA (22). Por isso, essas são as duas fases do ciclo celular (G2 e M) em que as células são mais radiossensíveis (13,22,23,25).

Além de danos ao DNA, outros mecanismos de danos celulares também são possíveis com uso de radiação ionizante que induzem morte celular. O tipo de morte celular induzida por radiação ionizante depende do tipo de célula, do estágio no ciclo celular, da capacidade de reparo de danos no DNA, da dose de radiação ionizante e

do microambiente celular (13,22,26). Isso pode ocorrer por meio de mecanismos diretos ou indiretos.

O mecanismo direto de morte celular induzida por radioterapia ocorre pela absorção de energia pelo meio biológico celular, que interage diretamente com o DNA e proteínas, causando danos que podem ocorrer até um tempo após a irradiação tecidual (23,25,26). No mecanismo indireto, a radiação ionizante interage com moléculas que constituem o meio da célula, principalmente água, aumentando a concentração de radicais livres que são capazes de aumentar a radiossensibilidade e promover danos celulares (23,25). Quebras de fita dupla de DNA também podem ser induzidas por espécies reativas de oxigênio, que são naturalmente produzidas durante o metabolismo celular (13). A figura 1 mostra os principais genes envolvidos na reposta celular induzida por radiação ionizante por meio de mecanismos diretos e indiretos de morte celular.

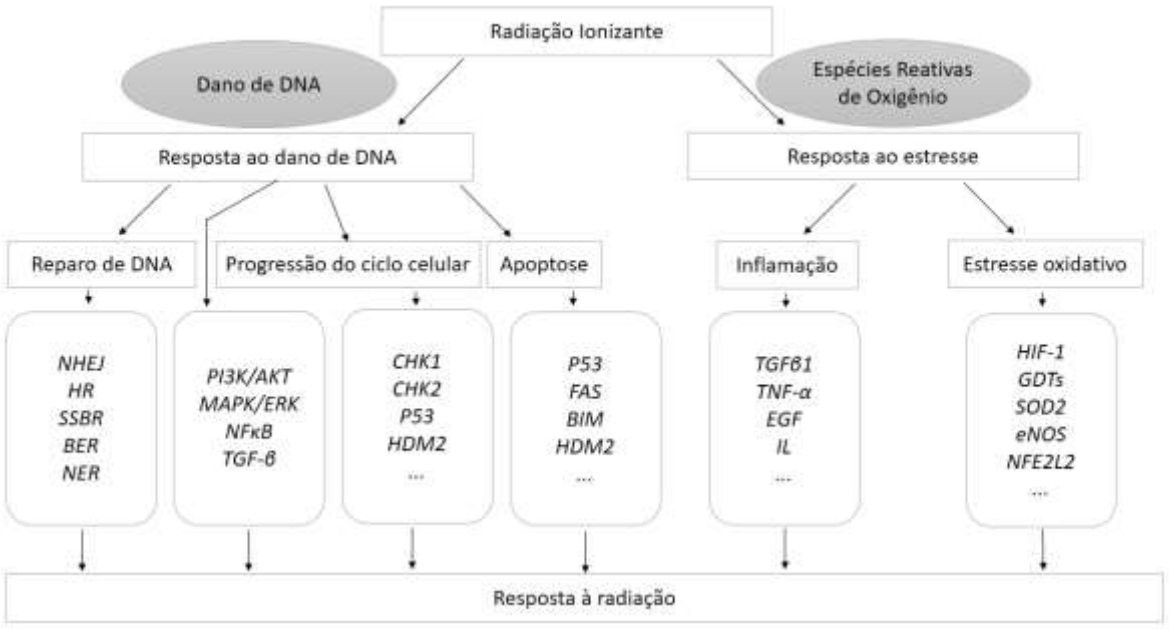


Figura 1 - Genes envolvidos nos mecanismos direto e indireto de lesão celular induzidos por radiação ionizante. Fonte: Guo et al (2015) (27) traduzida.

O reconhecimento da lesão do DNA induzido por radiação ionizante promove a ativação de uma cascata de sinalizadores que definirão, a depender de seu

funcionamento, se a célula será reparada, progredirá no ciclo celular ou sofrerá apoptose (27). Além disso, o aumento da concentração de espécies reativas de oxigênio pode ativar genes que induzirão inflamação tecidual ou aumentarão o estresse oxidativo e terão, por conseguinte, efeito na radiossensibilidade (27). A cascata de inflamação também pode ser induzida pela exposição à radiação ionizante (4).

A resposta celular à radiação também é regulada por cascatas de ativação de genes e proteínas de transdução do sinal, que envolvem as vias PI3K / AKT, MAPK / ERK, NFκB e TGFβ (27). O complexo *MRE11-RAD50-NBS1* e os genes *53BP1, γ H2AX e MDC1* são reparadores de fragmentos das extremidades do DNA (27). Os genes *ATR* e *ATM* são responsáveis por ativar os processos de reparo de DNA, após quebra de fita dupla, pela recombinação homóloga e união de extremidade não homóloga, respectivamente (26-28). Esses genes também interagem com outros que são *checkpoints* essenciais para verificar a integridade do material genético nas fases do ciclo celular (Figura 2) (27,28). Se a lesão ao DNA for significativo, acontece a morte celular (26).

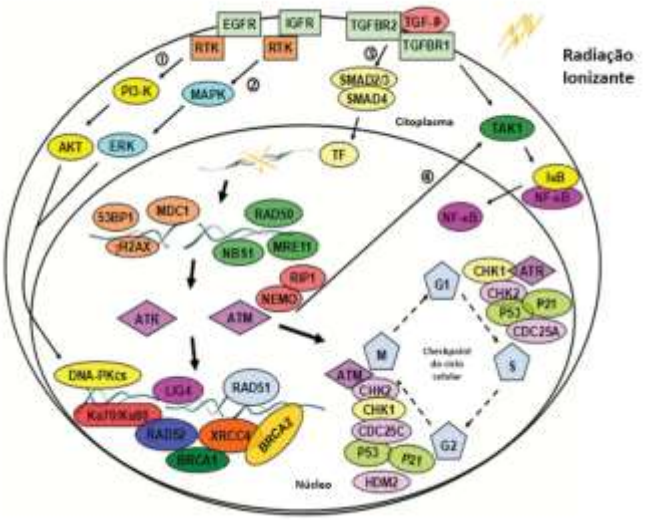


Figura 2 - Genes envolvidos no processo de reparo do DNA por diferentes vias de transdução do sinal, após exposição à radiação ionizante. Fonte: Guo et al (2015) (27) traduzida.

Qualquer mudança na função dos genes que participam dessas vias influenciará no reparo do DNA, na progressão no ciclo celular e na morte celular por apoptose.

Considerando que as células tumorais se multiplicam mais rápido do que células de tecidos normal, as primeiras tendem a passar mais vezes pela fase G2 e M do ciclo celular. Para que a radioterapia seja efetiva em controlar o crescimento e a multiplicação de células tumorais, a dose de radiação ionizante total planejada é subdivida, ou seja, fracionada em doses diárias para que haja oportunidade de atingir o maior número de células tumorais nas fases do ciclo celular em que elas estão mais radiossensíveis. Por isso, é realizado o fracionamento de dose.

2.2.2. Fracionamento de Dose e Evolução da Técnica de Radioterapia Externa

Os regimes de fracionamento de radioterapia têm como objetivo atingir o maior número de células tumorais em fases do ciclo celular mais radiossensíveis (G2 e M), aumentando o efeito terapêutico da radiação ionizante.

A dose de radiação ionizante absorvida por unidade de massa na radioterapia é descrita como *Gray* (Gy) (24). Desde a primeira dose de radiação ionizante já são gerados radicais livres, espécies reativas de oxigênio, quebra de fita dupla de DNA e recrutamento da cascata de inflamação (4). O fracionamento da dose total também tem como objetivo minimizar os efeitos adversos em tecidos sadios adjacentes ao tumor (24).

As técnicas de radioterapia externa evoluíram para reduzir o campo de incidência da radiação ionizante para o mais restrito possível ao tumor. O planejamento, que antes era realizado com base em parâmetros ósseos obtidos em radiografias, passou a ser feito com imagens tomográficas em 3 dimensões e a entrega de dose pode ser feita, hoje, por técnicas de intensidade modulada (24). A radioterapia por intensidade modulada é uma técnica que permite mensurar a dose de radioterapia que será entregue ao tumor, à margem tumoral e aos tecidos sadios adjacentes (5,22). Dessa forma, é possível mensurar a probabilidade de lesão tecidual em tecidos saudáveis e minimizar reações adversas (5,22).

Toxicidades decorrentes da exposição à radiação ionizante ainda são muito comuns (4,5). Considerando que alguns tecidos sadios também tem alta capacidade

de proliferação, como pele e mucosas, as doses fracionadas também atingem esses tecidos promovendo reações adversas (4).

2.2.3. Radioterapia no Câncer de Mama

A radioterapia pós-mastectomia, ou adjuvante, é realizada no plastrão e nos linfonodos da fossa supra e infraclavicular e axila quando não foi feita ressecção dos linfonodos axilares (20). A radioterapia pós-cirurgia conservadora de mama, também chamada de lumpectomia ou quadrantectomia, é geralmente indicada na região de linfonodos axilares, supra e infraclaviculares e mamária e permite a preservação de órgãos (20,29).

No tratamento adjuvante do câncer de mama, a Sociedade Brasileira de Radioterapia (SBRT) recomenda que a radioterapia externa seja convencionalmente realizada com uma dose total que varia de 45,0 a 50,4 Gy no leito tumoral, fracionada em 1,8 a 2,0 Gy por dia, cinco dias por semana, durante 5 a 6 semanas de tratamento (13,30,31). Em regimes de hipofracionamento, que também têm sido utilizados para o tratamento de câncer de mama, a SBRT recomenda uma dose total de 40,0 a 42,5 Gy, administrada em frações de 2,66 a 3,3 Gy ao dia, 5 vezes por semana (30).

A técnica de *boost* é caracterizada pelo uso de uma dose de reforço de radiação ionizante sobre o leito tumoral depois de ter concluído a radioterapia para melhorar o controle local (21). A dose é de 10 a 16 Gy e pode ser administrada de 2 a 2,5 Gy por dia (20). No tratamento do câncer de mama a radioterapia intra-operatória em dose única também pode ser utilizada (16,20).

2.2.4. Efeitos Adversos da Radioterapia

Os efeitos adversos da radioterapia são caracterizados por reações que ocorrem em tecidos adjacentes ao tumor ou que têm contato com a radiação ionizante durante a administração da dose. Esses efeitos adversos podem ser agudos ou crônicos dependendo do tempo de surgimento (13).

Efeitos adversos agudos surgem durante a radioterapia, ou até 3 meses após o término, em tecidos com alta capacidade de proliferação (13,22,32). Tecidos como pele e mucosas, por exemplo, são frequentemente afetados (22,23,32). Já os efeitos crônicos surgem de 3 meses após o término da radioterapia até anos depois, afetando tecidos compostos por células com menor capacidade de proliferação, como o tecido cardíaco, muscular e subcutâneo, por exemplo (13,22,23,32).

Dependendo da gravidade das reações agudas, pode ser necessário interromper o tratamento (13). Essas reações causam dor e desconforto e podem causar impacto na qualidade de vida dos pacientes (22). A radiodermatite aguda é um efeito adverso muito comum em pacientes com câncer de mama.

2.3. RADIODERMATITE AGUDA

A radiodermatite aguda é uma reação cutânea com alta incidência que acomete pacientes com câncer submetidos à radioterapia durante e até três meses após o fim do tratamento (9,10). Cerca de 95% de pacientes com câncer apresentam algum grau de radiodermatite aguda durante a radioterapia, sendo muito frequente em pacientes tratadas para câncer de mama (6,7,33). Estima-se que os primeiros efeitos da radiação ionizante sob o tecido cutâneo apareçam de 2 a 4 semanas após a primeira dose de radioterapia (6).

A radiodermatite aguda geralmente inicia com hiperpigmentação da área irradiada, seguida por eritema leve e/ ou transitório, eritema intenso, descamação seca, descamação úmida e, em casos mais graves, pode levar a hemorragia, necrose e / ou ulceração (Figura 3) (6). Geralmente, quando os pacientes apresentam descamação úmida disseminada é feita a interrupção da radioterapia para que o tecido cutâneo não evolua para reações mais graves.

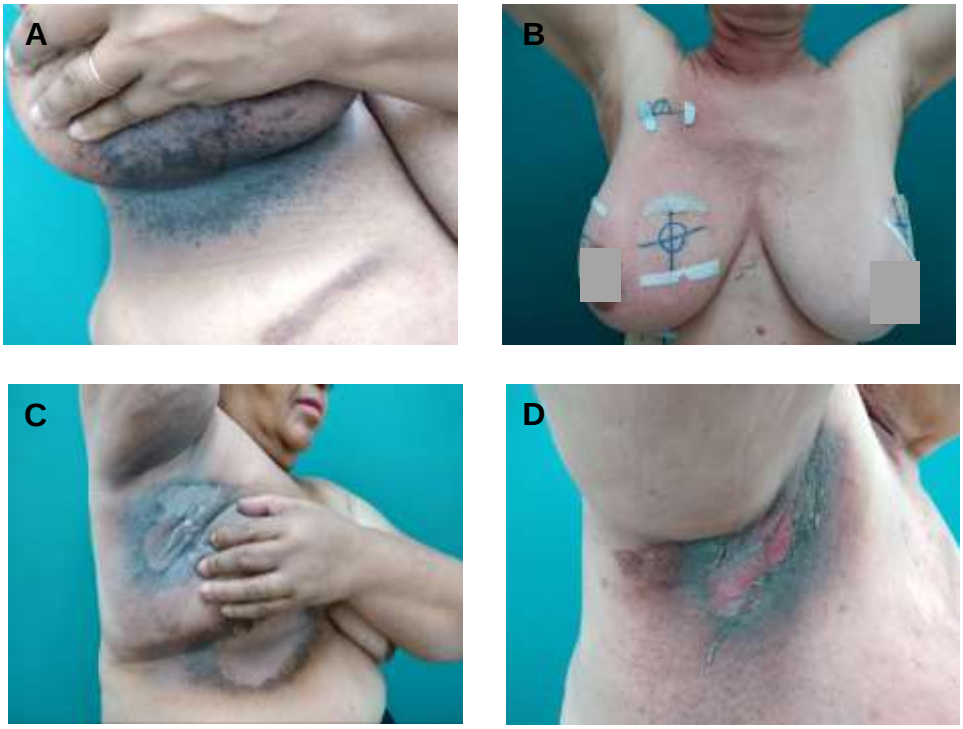


Figura 3 – Sinais de radiodermatite aguda em pacientes com câncer de mama: A) Hiperpigmentação; B) Eritema; C) Descamação Seca; D) Descamação Úmida. Fonte: Acervo digital do Laboratório Interdisciplinar de Pesquisa Aplicada à Prática Clínica em Oncologia (LIONCO).

2.3.1. Fisiopatologia

Assim como a radiação ionizante age sobre o tumor, por mecanismos de lesão ao DNA diretos e indiretos, o mecanismo fisiopatológico de desenvolvimento da radiodermatite aguda ocorre da mesma maneira. Os efeitos da radioterapia sobre o tecido cutâneo são cumulativos e se somam a cada fração de radiação ionizante recebida (6,8).

O mecanismo de lesão tecidual ocorre por alterações na fita dupla de DNA das células epiteliais ou por meio do aumento de espécies reativas de oxigênio no meio intracelular (6,7). As lesões causadas principalmente às células basais da epiderme, que não conseguem se autorrenovar em um tempo suficiente para reconstituir o tecido (6). Além disso, a radiação ionizante promove ativação da cascata inflamatória no tecido cutâneo (6-8).

A hiperpigmentação da pele ocorre devido a um estímulo excessivo de produção de melanina desencadeado pela exposição à radiação ionizante (6,10). Eritema local inicia logo após a primeira fração de radioterapia e é mais intenso por volta da segunda semana, em decorrência de vasodilatação e aumento da permeabilidade vascular (6,9,10). Em seguida, inicia uma reação inflamatória com liberação de quimiocinas e citocinas (principalmente interleucinas e TNF-α) que controlam a adesão de células endoteliais e recrutam células imunes (6). Esse processo pode ser percebido com a manifestação de eritema intenso (6).

A descamação seca geralmente surge por volta de 30 Gy de dose acumulada (10), entre a terceira e quarta semana (9), e acontece em decorrência de uma tentativa compensatória rápida de renovação de células basais epidérmicas, que ocorre mais rápido do que a eliminação de células epidérmicas que sofreram lesão (6). Associada a isso, a radioterapia também promove lesões nas células das glândulas sebáceas e dos folículos pilosos, o que causa aumento do ressecamento da pele e perda de pelos na área tratada (6). Quando toda a camada basal é destruída ocorre a descamação úmida, por volta de 4 a 5 semanas de tratamento (9), com rompimento de barreira e produção de exsudato (6).

É importante ressaltar que essas reações celulares serão observadas no campo da pele correspondente ao campo que está sendo irradiado e não necessariamente precisam acontecer gradativamente. Além disso, o tempo de aparecimento de cada grau de reação pode variar entre os pacientes. Geralmente são usadas escalas para mensurar e acompanhar a evolução do grau de radiodermatite ao longo do tratamento.

2.3.2. Escalas de Avaliação

Existem várias escalas de graduação da radiodermatite. Na clínica, a escala do *National Cancer Institute* (NCI), conhecida como *Common Toxicity Criteria for Adverse Events* (CTCAE) (34), e a escala do *Radiation Therapy Oncology Group* (RTOG) (35) são as mais utilizadas (Tabela 2).

Tabela 2 – Graduação de radiodermatite de acordo com a reação da pele. Fonte: Kole et al (2017) (9), adaptada e traduzida.

	Reação na pele	
Grau RD	CTCAE v 5.0	RTOG
0	Nenhuma reação	Nenhuma reação
1	Eritema leve ou descamação seca	Eritema leve, descamação seca, perda de pelo, diminuição de sudorese
2	Eritema moderado a intenso, descamação úmida local confinada a dobras cutâneas, edema	Eritema moderado ou intenso, descamação úmida local, edema moderado
3	Descamação úmida disseminada, sangramento induzido por abrasão	Descamação úmida disseminada e em dobras cutâneas, edema grave
4	Consequências com risco de vida, necrose, ulceração, sangramento espontâneo	Ulceração, hemorragia, necrose
5	Morte	Morte

RD= radiodermatite; CTCAE V5.0 = *Common Toxicity Criteria for Adverse Events* versão 5.0 (34); RTOG = *Radiation Therapy Oncology Group* criteria (35).

2.3.3. Manejo Clínico

Várias orientações de cuidados usuais da pele são bem documentadas na literatura e devem ser orientadas aos pacientes com câncer antes de iniciar a radioterapia, como por exemplo: higiene diária da área irradiada com uso de sabonete neutro e água morna sem atrito sob a pele; secar delicadamente; manter a área de tratamento protegida da exposição solar e usar roupas mais folgadas que evitem atrito (7,9,10); uso de desodorantes em pacientes que recebem radioterapia em mama tem dados controversos na literatura mas, de acordo com o *guideline* da *Oncology Nursing Society* (ONS) (14), pode ser recomendado ou não; entre outros.

Apesar de haver várias recomendações de cuidados com a pele da área tratada antes e durante a radioterapia, essas medidas não previnem definitivamente o desenvolvimento de radiodermatite aguda. No entanto, ainda não há consenso na literatura sobre produtos que sejam efetivos para prevenir essa reação (13,14,36). Por isso, o uso de mecanismos preditores do desenvolvimento de radiodermatite aguda seria uma ferramenta útil para melhorar o planejamento do tratamento.

2.3.4. Fatores de Risco e Radiossensibilidade Individual

Alguns fatores de risco predispõem os pacientes submetidos à radioterapia a desenvolver radiodermatite aguda grave, sendo:

- Fatores relacionados ao tratamento – volume da área tratada, localização do tumor (superficial ou profundo), dose total de radiação ionizante, dose fracionada, duração do tratamento, uso de *boost* e combinação com outras modalidades de tratamento para o câncer (6,9,15);
- Fatores relacionados ao paciente **-** exposição à radiação solar (UVA e UVB), dobras cutâneas, umidade na região irradiada, tabagismo, etilismo, estado nutricional, Índice de Massa Corporal (IMC), sensibilidade da pele exposta, doenças de pele pré-existentes e fatores genéticos (6,9,15).

Em pacientes com câncer de mama, as áreas com maior risco de radiodermatite são pregas inframamária e axilar, devido a maior umidade local e probabilidade de fricção pele-a-pele ou mesmo com roupas (9,15). Além disso, a idade, o volume mamário e IMC podem aumentar o risco de desenvolver radiodermatite aguda severa em pacientes com câncer de mama (15).

Os fatores de risco de radiodermatite podem ser considerados como fatores determinantes de radiossensibilidade individual. A radiossensibilidade se refere a suscetibilidade aos efeitos adversos decorrentes da exposição à radiação ionizante. Estima-se que mais de 45% dos pacientes com câncer de mama tenham elevada radiossensibilidade intrínseca (13).

Um dos desafios de planejar o tratamento de pacientes com câncer está na identificação desses fatores que influenciam no aumento da radiossensibilidade

individual e na diminuição da capacidade de reparo dos tecidos (5,22,37). Porém, pacientes com fatores de risco e regimes de tratamento semelhantes podem apresentar graus de radiodermatite bem diferentes entre si. Na literatura, já se discute que fatores genéticos podem influenciar a resposta dos tecidos à radiação ionizante (5).

2.4. MARCADORES GENÉTICOS E RADIOTOXICIDADE

As pesquisas sobre fatores que influenciam no desenvolvimento de reações adversas à radioterapia têm investigado quais seriam as contribuições de fatores genéticos nessas reações (38). Essa hipótese surgiu a partir da descoberta de síndromes que tornam os indivíduos mais sensíveis à radiação ionizante, como a Síndrome Ataxia-Telangectasia, decorrentes de mutações em genes que respondem às agressões ao DNA e ao reparo (39,40).

Com isso, a Radiogenômica surgiu como área de estudo que visa identificar biomarcadores que sejam capazes de predizer reações adversas em pacientes com câncer submetidos à radioterapia, ou identificar indivíduos que têm maior suscetibilidade de desenvolver grau severo dessas reações (22,41,42). Biomarcadores são substâncias que podem ser mensuradas em amostras de biópsias, fluidos corporais e fezes para indicar o estado de funcionamento de processos metabólicos normais, de doenças e de respostas a um determinado tratamento (22,43).

Em 2009 foi estabelecido o *Radiogenomics Consortium (Manchester, United Kingdom*), apoiado pelo *National Cancer Institute* (NCI) (44), que contou com a participação de 133 instituições de 33 países em 2019 (45). O objetivo do *Radiogenomics Consortium* é estabelecer colaborações entre países para que estudos de associação entre biomarcadores e reações adversas à radioterapia sejam realizados em grandes coortes (41,46). Desse modo, espera-se identificar vias moleculares que participam do desenvolvimento das reações adversas à radioterapia

e identificar variantes no genoma que sejam capazes de prever o desenvolvimento e a gravidade dessas reações (41,44,45,47).

Os principais biomarcadores estudados pelo *Radiogenomics Consortium* são os Polimorfismos de Nucleotídeo Único (SNP) (45,48). Os SNP são considerados bons marcadores genéticos, nos estudos de associação com características fenotípicas, por serem frequentes nas populações e facilmente genotipados (49). Além disso, a amostra coletada dos pacientes para pesquisa de SNP pode ser obtida de qualquer tecido normal, uma vez que os polimorfismos estão presentes em todas as células normais, incluindo células sanguíneas (47).

2.4.1. Polimorfismo de Nucleotídeo Único

A sequência de DNA de quaisquer dois indivíduos do mundo é cerca de 99,9% semelhante entre eles (50,51). Variantes em apenas 0,1% do genoma, referente a aproximadamente 1 par de bases em uma sequência de 1.000 nucleotídeos, torna os indivíduos fenotipicamente diferentes entre si (22,51-53). Desse 0,1% de variantes no genoma, cerca de 99% são devido a polimorfismos de nucleotídeo único (54).

Tanto as mutações quanto os polimorfismos de nucleotídeo único, do inglês *Single Nucleotide Polymorphisms* (SNPs), são variantes genéticas que estão presentes em um ponto específico na sequência de DNA. Contudo, os SNPs são consideravelmente comuns na população e têm probabilidade de 1% ou mais de serem identificados em um indivíduo, enquanto a “mutação genética” refere-se às variantes no DNA que estão presentes em menos de 1% da população (50,51). Apesar dessas definições serem bem estabelecidas, essas nomenclaturas ainda causam confusão (50). Condit et al (2002) (55) sugerem o uso do termo “variante genética” ou “alteração genética” para substituir as definições de mutações e polimorfismos que, podem ser complementados com os termos patogênico ou benigno (50,56). No entanto, o estabelecimento de uma nomenclatura generalista ainda tem sido discutido.

SNPs são variantes genéticas que ocorrem, com a substituição de um único nucleotídeo na sequência do genoma (40). A variação que originará o SNP pode ocorrer tanto em regiões não codificantes que não promoverão alterações fenotípicas, como as regiões intergênicas e de *íntrons*, quanto na região codificante, de *éxon*,

podendo modificar ou não a função do gene e consequentemente o fenótipo (Figura 4) (49,51,57). Apesar da troca de nucleotídeo em uma posição específica poder ser feita por qualquer outro (C, G, A ou T), geralmente os SNPs são bialélicos (49,58).

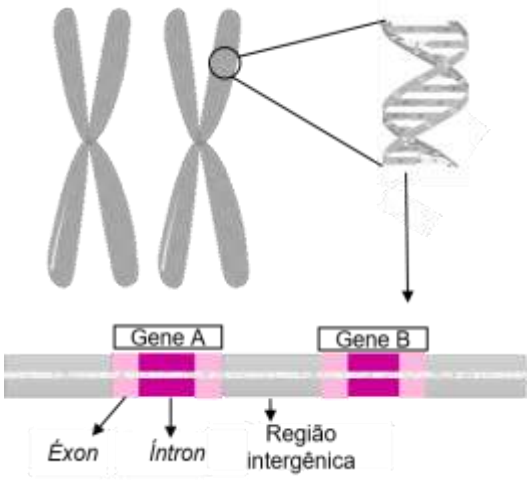


Figura 4 – Representação esquemática da região não codificante (*íntron*) e codificante (*éxon*) de um gene. Fonte: Autoria própria, baseada na representação esquemática de Alberts et al (2017) (59) p.471.

Para compreender como os SNPs ocorrem no DNA e qual o impacto deles no fenótipo, vejamos o seguinte exemplo:

No cromossomo 19, o *locus* que codifica o gene *TGFβ* apresenta, mais comumente, no *éxon* 1, um nucleotídeo de Guanina (G) na posição 869. Na fita complementar de DNA essa G vai parear com uma Citosina (C) codificando um aminoácido de Prolina (Pro) no códon 10 (Figura 5A). Por ser encontrado com maior frequência na população, a C, neste exemplo, é chamada de alelo selvagem. No entanto, alguns indivíduos apresentam uma troca de G por Adenina (A) nesta posição (Figura 5B). Essa troca também leva a uma mudança na fita complementar de DNA, ou seja, atroca de C por Timina (T), codificando agora um aminoácido de Leucina (Leu) (Figura 5C). O alelo T é chamado de alelo variante, neste exemplo, por ser menos frequente na população. Como esta variação alélica (A>G) está presente em mais de 1% da população, ela é chamada de SNP. Este SNP de *TGFβ* é descrito como Pro10Leu ou codificado como rs1800470.

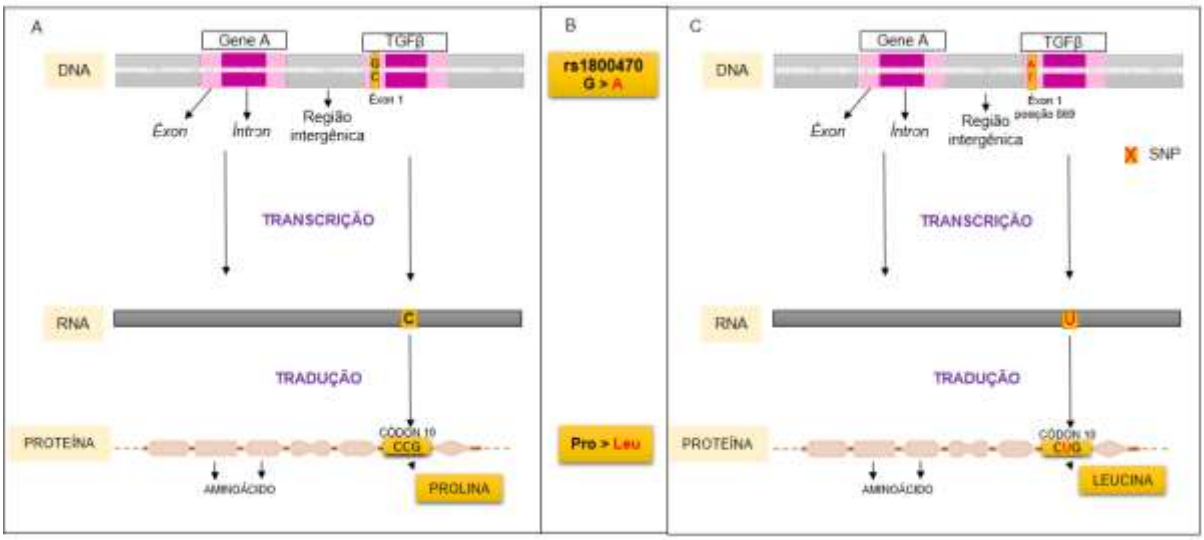


Figura 5 – Representação esquemática do SNP rs1800470 no gene *TGFβ.* A) A sequência de nucleotídeo que compõe o gene *TGFβ* será transcrita em RNA e uma das fitas será traduzida em uma proteína que possui um aminoácido de Prolina (Pro) no códon 10; B) rs code do SNP em *TGFβ (*rs1800470) e a respectiva troca de base (G>A) e de proteína (Pro>Leu); C) SNP ocorre na posição 869, do éxons 1, do gene *TGFβ (G>A)* e origina uma fita complementar com uma Timina nesta posição. A Timina será traduzida em Uracila que dará origem à um aminoácido de Leucina (Leu) no códon 10. Fonte: Autoria própria.

O genoma humano é diploide, ou seja, herdamos 23 cromossomos do pai e 23 da mãe, que se organizam em pares por semelhança entre si. Essa organização em pares de cromossomos semelhantes é chamada de cromossomos homólogos e eles possuem sequências de nucleotídeo muito parecidas. Assim, o SNP pode ocorrer em um dos cromossomos ou no par de cromossomos homólogos. Dessa forma, podemos classificar como: homozigoto para alelo selvagem, homozigoto para alelo variante ou heterozigoto (Figura 6).

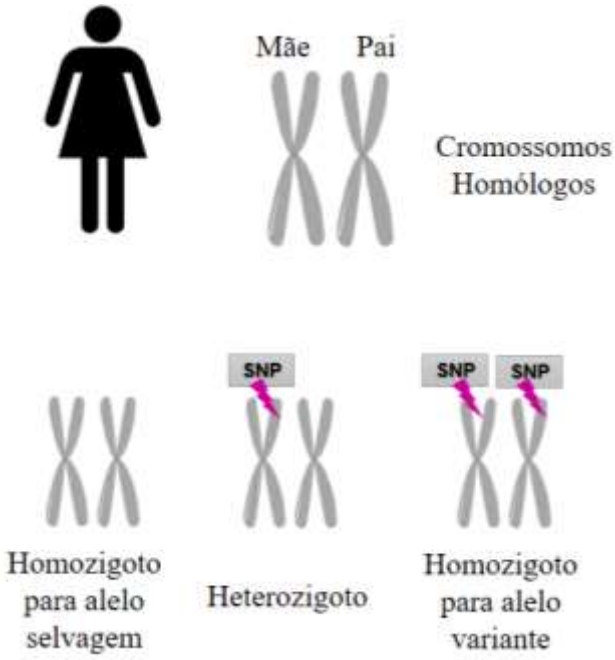


Figura 6 – Classificação de acordo com ocorrência de SNP nos cromossomos homólogos. Fonte: Autoria própria.

2.4.2. Variação de SNPs em Diferentes Etnias

Os SNPs também são usados para diferenciar grupos étnicos devido as características fenotípicas apresentadas ao longo da evolução e processo de seleção natural (60). Huang, Shu & Cai (2015) (52) realizaram um estudo para esclarecer a frequência de SNPs em diferentes populações e encontraram que 299 SNPs apresentaram frequência de variação estatisticamente significativa em diferentes etnias. A frequência de alelos de SNPs em uma população pode variar de acordo com a localização geográfica, etnia e ancestralidade (53,61). Por isso, é importante considerar a prevalência dos SNPs em diferentes regiões geográficas em análises de associação com eventos adversos (60). Análises genômicas devem considerar essa variável para que dados não sejam extrapolados para todas as populações.

2.4.3. Associações Baseadas em Haplótipos

Os SNPs podem aparecer também em haplótipos. Haplótipos são combinações de alelos, ao longo de um único cromossomo, que estão dispostos em *locus* muito próximos entre si e organizados em blocos (62). Esses blocos de alelos raramente são separados no processo de recombinação e são passados entre as gerações (62). Dessa forma, os SNPs que ocorrem em haplótipos podem ser herdados juntos nas gerações subsequentes (40). As análises de associação de haplótipos com características fenotípicas são capazes de mostrar os potenciais efeitos da interação entre variantes alélicas em blocos e mudanças no fenótipo (61).

2.4.4. Técnicas de Estudo de Polimorfismos de Nucleotídeo Único

A técnica de estudo de genes candidatos tem sido utilizada para avaliar a associação entre SNPs e reações adversas à radioterapia. Para isso, é feita a seleção de genes que já são conhecidos por participar do mecanismo molecular de desenvolvimento das reações adversas (53,63). Seibold et al (2015) (64) realizaram um estudo de genes candidatos, envolvidos no estresse oxidativo, para verificar a capacidade de predizer toxicidade tardia em 753 pacientes com câncer de mama que realizaram radioterapia. O estudo mostrou que pacientes com câncer de mama portadores de alelo raro para o SNP rs2682585 no gene *XRCC1* apresentaram menor ocorrência de toxicidades cutâneas tardias (OR: 0,77; IC 95%: 0,61-0,96; p=0,02) (64). A associação desse SNP com toxicidade de pele tardia, em pacientes com câncer de mama submetidos à radioterapia, foi validada pelos membros do *Radiogenomics Consortium* (42). O grande desafio do desenvolvimento de pesquisas como essa é que os pesquisadores devem ter conhecimentos de base sobre biologia molecular e os efeitos da radiação ionizante sobre o DNA (40).

Outras técnicas que investigam genes de suscetibilidade, como a *Genome-Wide Linkage Studies* (GWLS) e *Genome-Wide Association Studies* (GWAS), são usadas para investigar todos os genes, de forma mais ampla, e não somente aqueles já conhecidos por participar das vias moleculares de desenvolvimento da doença

estudada (51). Essas técnicas se baseiam na varredura completa do genoma e são extremamente úteis na investigação de polimorfismos que podem estar associados com reações adversas à radioterapia (53,63). No entanto, ainda são pouco usadas nos estudos de associação de polimorfismos e radiodermatite aguda. O *Radiogenomics Consortium* tem por objetivo conseguir recursos para que as avaliações em grandes coortes sejam realizadas por técnica de GWAS (44,46).

2.5. IMPORTÂNCIA DE ESTUDOS DE POLIMORFISMOS DE NUCLEOTÍDEO ÚNICO PARA PREDIZER RADIODERMATITE EM PACIENTES COM CÂNCER DE MAMA

Como já descrito anteriormente neste trabalho, o Instituto Nacional do Câncer estima que 66.280 novos casos de câncer de mama em mulheres sejam diagnosticados no ano de 2020 (1). A maioria das mulheres com câncer de mama são diagnosticadas em estágios iniciais (65,66). O tratamento cirúrgico frequentemente é feito por cirurgia conservadora de mama e radioterapia adjuvante, em casos diagnosticados em estágios iniciais, ou mastectomia associada à radioterapia adjuvante, quando a paciente apresenta câncer de mama localmente avançado (65,67). Estima-se que cerca de 50-60% de todos os pacientes com câncer de mama sejam tratados com radioterapia em algum momento do planejamento de tratamento oncológico (68). Desses pacientes tratados com radioterapia, cerca de 95% apresentam algum grau de radiodermatite aguda (68). Dependendo da gravidade dessa reação pode ser necessário interromper a radioterapia para permitir a recuperação do tecido cutâneo (68).

Graus severos de radiodermatite podem causar dor, queimação e ardor local, além de ter grande impacto na qualidade de vida e na imagem corporal das pacientes (68,69). Considerando essas estimativas, métodos capazes de predizer a ocorrência e/ou severidade de radiodermatite aguda poderiam melhorar o planejamento de radioterapia. Além de ter como base dados clínicos do tumor e dados basais de características das pacientes, como a exposição a fatores de risco para

radiodermatite, a avaliação de SNPs que possam predizer radiodermatite poderia auxiliar no acompanhamento das pacientes e permitir um planejamento de radioterapia personalizado.

Dessa forma, a identificação prévia de suscetibilidade de radiodermatite pode ter impacto positivo na qualidade de vida das pacientes, que poderiam apresentar radiodermatite severa, e nos custos para o serviço de saúde com manejo dessa radiotoxicidade.

3 OBJETIVOS

3.1. OBJETIVO GERAL

Revisar a literatura e avaliar a certeza de evidência do potencial de polimorfismos de nucleotídeo único predizer radiodermatite aguda em pacientes com câncer de mama submetidas à radioterapia.

3.2. OBJETIVOS ESPECÍFICOS

- Identificar na literatura estudos que avaliam polimorfismos de nucleotídeo em pacientes com câncer de mama submetidas à radioterapia;
- Mensurar a prevalência de polimorfismos de nucleotídeo em pacientes que desenvolveram radiodermatite aguda;
- Verificar se existe associação entre polimorfismos de nucleotídeo e o desenvolvimento de radiodermatite severa;
- Avaliar a qualidade metodológica dos estudos individuais incluídos na revisão e a certeza da evidência a partir da síntese dos dados.

4 NOTA INFORMATIVA

Esta revisão sistemática será apresentada em formato de artigo e, posteriormente, será enviada para publicação na revista *International Journal of Radiation Oncology, Biology, Physics*, ISBN: 0360-3016, Fator de Impacto 7.038 (2020), Qualis CAPES A1. Segundo as normas da revista, tabelas e figuras devem ser apresentadas em documentos separados. Com o intuito de melhorar a leitura desta dissertação, as figuras e tabelas serão incluídas no corpo do texto após a primeira citação. A indicação de primeiro, segundo e terceiro revisor será removida do corpo do artigo no momento da submissão do artigo, seguindo as recomendações de garantia de anonimato da pesquisa. O protocolo da revisão foi enviado ao *International Prospective Registry of Systematic Reviews (PROSPERO).* Porém, até o momento, não foi registrado.

5 ARTIGO

Single nucleotide polymorphisms to predict acute radiation dermatitis in breast cancer patients: A systematic review and meta-analysis

SNPs to predict acute radiation dermatitis

5.1. ABSTRACT

Purpose: To identify Single Nucleotide Polymorphisms (SNPs) that can predict the occurrence of acute Radiation Dermatitis (RD) in breast cancer patients undergoing radiotherapy, and the association between SNPs and severe RD. **Methods:** A systematic review was performed using seven databases and the gray literature. We performed a proportion meta-analysis to assess the frequency of the SNPs in patients with RD, and meta-analysis to evaluate the association between SNP and occurrence of severe RD. **Results:** We included sixteen cohort studies. Thirteen studies presented low risk of bias, and three moderate risk of bias. The two most prevalent SNPs in breast cancer with RD were the SNP rs1800469 in the *TGFβ1* gene (41%), and the SNP rs3957356 in the *GSTA1* gene (36%). The association meta-analysis of the SNPs and RD severity showed that seven genotypes in SNPs were associated with severe RD (*PTTG1* rs3811999-CC; *PTTG1* rs2961950-AA; *MAD2L2* rs2294638-GG; *MAT1A* rs2282367-GG; *GSTA1* rs3957356-CT; *CD44* rs8193-CT; *SH3GL1* rs243336-GC) and five SNPs were associated with lower RD (*PTTG1* rs2961952-GG; *CD44* rs8193-CC; *PTTG1* rs3811999-CT; *MAT1A* rs2282367-GA; *OGG1* rs2075747-AA). The CT genotype of the rs3957356 polymorphism in the *GSTA1* gene and the GG genotype of the rs2282367 polymorphism in the *MAT1A* gene showed low certainty of evidence, whereas. All other genotypes had very low certainty of evidence. **Conclusions:** Significant data show that SNPs genotyping may be a strategy for predicting RD in breast cancer patients. However, more studies need to be performed to confirm the prevalence data and the possible associations found in this review.

Keywords: Radiodermatitis; Radiotherapy; Genetic Markers; Breast Neoplasms; Systematic review; Meta-analysis.

5.2. INTRODUCTION

Radiotherapy (RT) is a therapeutic modality that uses beams of ionizing radiation and targets cells with a high capacity of proliferation (4). Approximately 50% of treatment protocols for breast cancer use RT (4,5). Although RT targets tumor cells, it also affects cells from adjacent tissues with a high proliferative capacity, such as the skin.

Acute radiation dermatitis (RD) is a skin reaction that affects approximately 95% of breast cancer patients undergoing radiotherapy (6,7). RD occurs by loss of proliferation capacity of the epidermal cells, dermis and vasculature accompanied by an inflammatory response and subsequent oxidative stress (6,7,70). Signals begin with changes in skin pigmentation, epilation, erythema, and dry desquamation, but may progress to moist desquamation, ulceration, hemorrhage, and necrosis (6). There is no consensus in the literature on products to prevent or to treat RD (13,14). This reaction affects the quality of life and, in severe cases from the development of disseminated moist desquamation, it may interrupt the radiation treatment (7,11).

Individual patient factors such as age, lifestyle, tumor location, and tumor size influence the severity of acute RD development (7,15). Although RD is a very common adverse effect, patients with similar treatment plan may show different tissues responses for the severity of RD due to the radiotherapy exposition. The hypothesis for this difference is that the radiosensitivity can be determined by the individual genetic variation (5,40).

In 2009, the Radiogenomics Consortium was created with the aim of establishing collaborative studies and large cohorts to investigate the association between genetic markers, mainly Single Nucleotide Polymorphisms (SNPs), and adverse reactions to radiotherapy (44). SNPs are genetic variants that occur by exchanging a single nucleotide in the DNA sequence that encodes a gene (40,49,51). SNPs are variant identified by DNA sequencing techniques that appear in at least 1% of the population (51). The identification of SNPs with predictive value for severe acute RD may offer the opportunity to develop personalized radiotherapy protocols based on individual radiosensitivity (5,43,46,53).

A previous meta-analysis evaluated an association between acute RD and polymorphism only in the *ERCC2* gene, also known as *XPD*, in patients with breast cancer and used a fixed effect, which does not consider an intrinsic heterogeneity of the sample (71). Another study evaluated the association between SNP in the *ATM* gene and *TP53* and radiotoxicity but did not individualize data for acute RD (72). Ghazali et al (2012) (73) performed a systematic review that included two studies evaluating genetic markers for acute RD. However, primary studies have already been published after this review. Zhao et al (2018) (74) performed a meta-analysis including different types of cancer to investigate an association between SNPs in the *XRCC1* gene and general tissue toxicity related to radiotherapy. However, they did not consider analyzing other genetic markers for tissue toxicity. No previous systematic reviews have individually evaluated an association between general SNPs with acute RD in breast cancer patients.

Thus, this systematic review and meta-analysis aims to identify SNPs that may predict the susceptibility of acute RD in breast cancer patients undergoing RT, and the association between SNPs and the occurrence of severe RD.

5.3. METHODS

This systematic review followed the criteria of the *Preferred Reporting Items for Systematic Reviews and Meta-analyses* (PRISMA 2020) checklist (75).

5.3.1. Elegibity Criteria

We included articles based in the PECOS acronym, in which: (P) Studies in breast cancer patients undergoing RT; (E) SNPs investigated in a sample obtained of the patient undergoing RT; (C) None or any control with a reference value for the SNPs (when available); (O) Capability of the SNPs to predict the developing or the severity of signals of acute RD; (S) Cohort studies in humans.

Studies were excluded for the following reasons: (1) Studies in patients with other types of primary cancer undergoing RT, that are not breast cancer; (2) Studies that include patients with different types of cancer undergoing RT do not show individual results for breast cancer patients; (3) No SNPs reported; (4) Studies that report analysis for RD evaluated after 3 months of the end of RT / chronic RD; (5) No association between SNPs and development of acute RD or severity of acute RD; (6) Studies that reported only association between SNPs and symptoms of acute RD, and not the signs; (7) Data not individualized for acute RD; (8) Experimental studies (*in vitro, in vivo* animal studies or clinical trials), descriptive studies, cross-sectional studies, case-control studies, reviews, letters, chapters, personal opinions, conference abstracts, thesis and dissertations; (9) Studies that did not report sufficient information.

5.3.2. Information Sources and Search Strategy

A search strategy was prepared and adapted for each eletronic databases using appropriate truncation and combination of the keywords, MeSH Terms and DeCS Terms referring to population, exposure, and outcome of the acronym PECOS. All

authors reviewed the strategy. We performed the search on seven electronic databases on May 31st, 2021, being: CINAHL, Cochrane CENTRAL, EMBASE, LILACS, PubMed, Scopus, and Web of Science. An additional, search of the gray literature was performed using Google Scholar, OpenGrey, and PROQUEST Thesis & Dissertations on the same day. There was no restriction on the year of publication or language. Reference manager *EndNoteBasic® software* (Thomson Reuters, USA) was used to collect the references and remove duplicates. More information about specific search strategy for each electronic databases is available in Appendix 1. If any conference abstract or thesis and dissertation could be eligible, we searched if the corresponding article has already been published to include in this review. A hand search of the reference of the included studies and in references cited in systematic reviews with similar topic was performed on June 23rd, 2021.

5.3.3. Selection Process

Two reviewers (BRLA and EBF) conducted independently conducted studies selection in two phases: In phase 1, titles and abstracts identified in search were screened using Rayyan software (76) and the references that met the eligibility criteria went on to the next selection phase. In phase 2, the same reviewers independently read full text of the studies selected in phase 1 and included in this review the references that were in accordance with the eligibility criteria. The first reviewer read the reference lists of the included studies and the reference lists of systematic reviews with a similar topic to look for articles that might have been missed in the search. Disagreements were resolved by consensus by the two reviewers and when necessary, a third reviewer (PEDR) was consulted for a final decision.

5.3.4. Data Collection Process

One reviewer (BRLA) collected data from the selected articles for this review. The second reviewer (EBF) checked all data obtained to confirm information. Any disagreements between the two reviewers were resolved by consensus and when

necessary, a third reviewer (PEDR) was consulted. When any data was not clear, the authors of the corresponding article were contacted for additional information.

5.3.5. Data Items

We recorded the following data from the included articles: study characteristics (author, publication year, and country), sample characteristics (sample size, age, and ethnicity), RT characteristics (dose and fraction), RD characteristics (scale for evaluation, lower/severe grade), genetic characteristics (sample collected, gene and SNPs studied, genotyping strategy, evidence of the Hardy–Weinberg equilibrium), and main conclusions.

For studies that reported more than one assessment of the grade of acute radiation dermatitis, we considered the highest grade reported to have been developed.

5.3.6. Study Risk of Bias Assessment

Two reviewers (BRLA and EBF) independently assessed the risk of bias of individual studies. Conflicts were resolved by consensus between the first and second reviewers. When necessary, a third reviewer (PEDR) resolved any conflicts. For this, the Critical Appraisal Checklist for Cohort Studies (77). For all tool questions, reviewers responded with yes, no, unclear or not applicable. Information justifying the judgment was recorded for each item of the tools used.

We categorized studies as high risk of bias if the study had 49% or less "yes" score, moderate risk of bias if the study had 50% to 69% "yes" score, and low risk of bias if the study had 70% or more of "yes" score.

5.3.7. Effect Measures

The primary outcome was the proportion of SNPs in breast cancer patients undergoing RT who had any degree of RD. Secondary outcome was the association

between studied SNPs and the development of lower or severe acute RD. Severe acute RD was considered as any manifestation of moist desquamation.

5.3.8. Synthesis Methods

SNPs evaluated in at least two studies were eligible for meta-analysis. We performed a qualitative synthesis of the main characteristics of the included studies. The proportion of each SNP in breast cancer patients with acute RD was assessed using *MetaXL 5.3 add-in Microsoft Excel software*. Prevalence data were presented by relative frequencies and 95% confidence intervals (95%CI). Association analysis of the SNPs and development of lower or severe acute RD was performed by subgroups of variant genotypes using *Cochrane Collaboration's Review Manager® 5.4 software (RevMan 5.4, Copenhagen, Denmark*). The summary measure was performed for odds ratio (OR) and 95%IC in dichotomous variables. To assess heterogeneity in the meta-analysis we used the inconsistency index (I^2), variance estimate of the real effects (Tau^2), and Cochran's Q 5% significance level (Chi^2).

5.3.9. Certainty of Evidence Assessment

The first and second reviewers (BRLA and EBF) independently assessed the certainty of evidence from the results obtained for the association of SNPs with acute RD in breast cancer patients. A third reviewer (PEDR) resolved all disagreements. For this, we use the Grading of Recommendation, Assessment, Development, and Evaluation (GRADE) criteria (78) which include: study design, risk of bias, inconsistency, indirectness, imprecision, and other considerations. The certainty of evidence for association analysis of each SNPs with severity RD was classified as high, moderate, low or very low. GRADEpro (79) was used to build the Summary of Finding (SoF) table.

5.4. RESULTS

5.4.1. Study Selection

We found 2,681 citations in electronic databases searching. Duplicate studies were removed, and 2,064 citations remained for analysis. The search in the gray literature obtained 345 citations. The full reading was performed for 64 articles from databases and 6 articles from gray literature. After evaluating, the articles for eligibility criteria, 48 articles from the databases and the 6 articles from gray literature were excluded (Appendix 2). Finally, sixteen articles (80-95) were selected for analysis. We did not find other eligible articles in the reference list of included studies nor in previous systematic reviews in the same topic. Figure 1 presents the detailed process of identification, selection, exclusion, and inclusion of the studies.

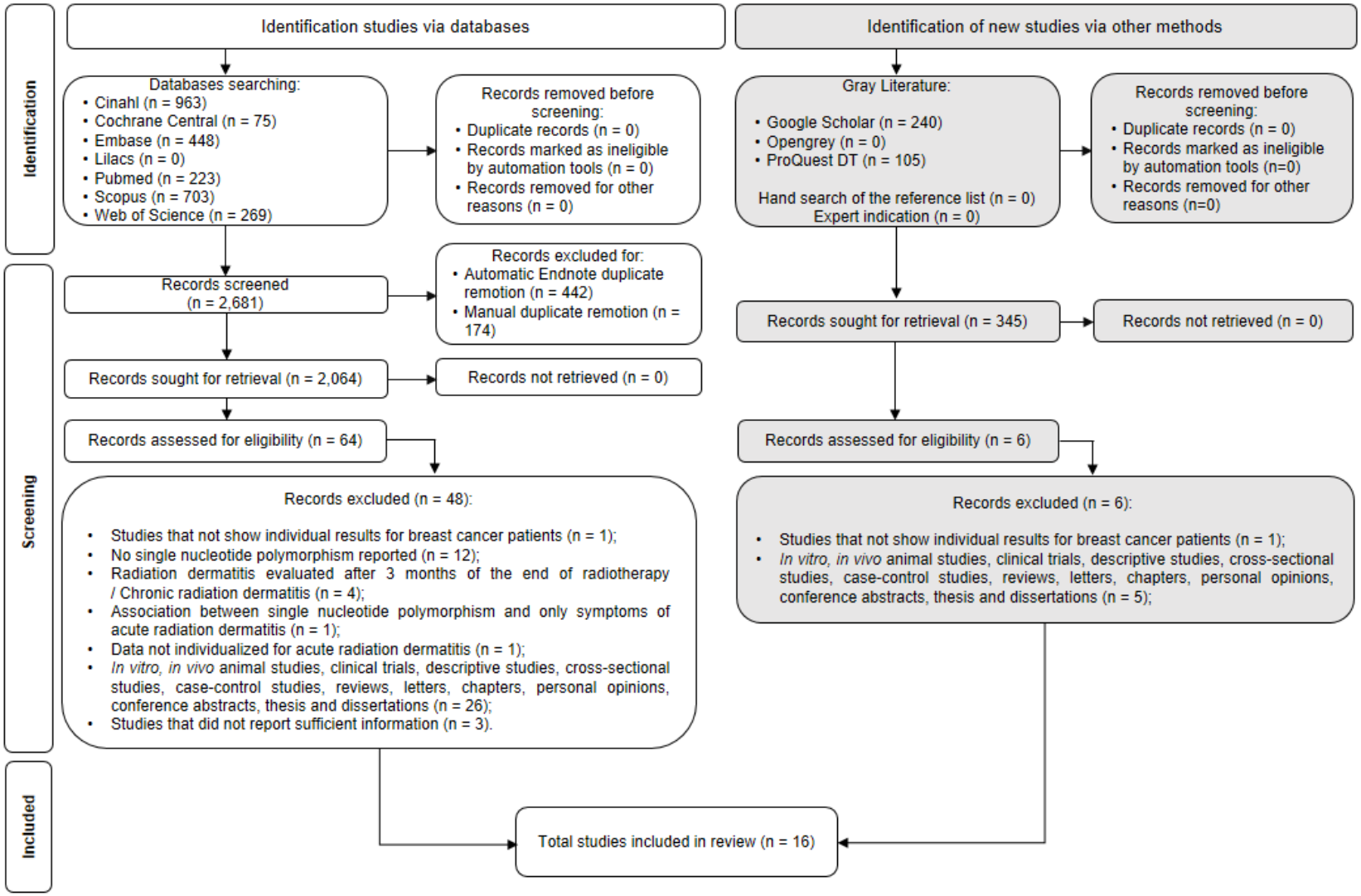


Figure 1 - Flow diagram of literature search and selection process. Adapted from PRISMA 2020 (75)

5.4.2. Study Characteristics

The included studies were published between 2005 and 2020, all in the English language. All studies are cohort, with fifteen studies prospectively following up patients (80-93,95) and one study is retrospective (94). A total of 4,742 breast cancer patients comprised the sample for this systematic review.

Surgical treatment for breast cancer was performed in all studies. The sample from three studies underwent mastectomy or breast-conserving surgery (86,88,89), in 11 studies (80-85,90-94) the sample underwent only breast-conserving surgery, and 2 other studies did not specify the type of surgery (87,95). In all studies patients received adjuvant radiotherapy. Regarding radiotherapy dose fractionation, in 11 studies patients underwent only conventional fractionation (80,81,83,84,88-91,93-95), in 4 studies (82,85-87) they received conventional or hypofractionated radiotherapy, and only one study (92) did not specify which was the fractionation. All studies collected blood samples from patients for genotyping and identification of SNPs, and additionally, two studies also collected oral swab (84,89).

The occurrence of RD was measured according to the highest degree presented by the patients. Skin assessment was performed using the *Common Terminology Criteria for Adverse Effects* (CTCAE) (34) scale in 10 articles (80,81,83,85,87,89,90,92,93,95), the *Radiation Therapy Oncology Group* (RTOG) (35) scale in 5 articles (82,84,88,91,94), and the Oncology Nursing Society (ONS) (14) scale in one article (86). Although the scales were different, all articles considered that moist desquamation, even in at least one area, was a manifestation of severe RD. The table 1 presents the main characteristics of the studies.

Table 1 - Summary of descriptive characteristics of the included studies (n = 16).

Study	Sample		RT	RD			Genetic evaluation			Main Results
Author, Year Country	**Sample size (n)**	**Mean age/ Range in years**	**RT dose (range)**	**Scale**	**Groups**		**Gene**	**SNP (rs code)**	**Genotyping strategy**	
					Lower RD (n)	**Severe RD (n)**				
Ahn et al, 2006 (80) Germany	446	60 / 26-87	BED Mean 54 Gy ±4.8 Gy (35.5-64.5)	CTCAE v 2.0 modified	CTCAE < 2c (369)	CTCAE ≥ 2c (77)	*CAT* *eNOS* *MnSOD* *MPO*		MALDI-TOF mass spectrometry	There were no significant associations between acute RD and any of the SNPs. In further analysis, associations between BMI ≥ 25 (overweight/obese) and severe acute RD were more pronounced among women with *eNOS* GG genotypes (HR: 6.39; 95% CI: 2.53-16.15) or *MPO* GG genotypes (HR: 3.61; 95% CI: 1.78-7.35). Multiplicative interactions between genotypes and BMI were not statistically significant (*eNOS* genotype; p: 0.25 and *MPO* genotype; p: 0.27). Women with both *MPO* GG and e*NOS* GG genotypes had increased (adjusted HR: 18.84; 95% CI: 2.50-142.00) of the severe acute RD. *CAT* and *MnSOD* genotypes did not modify associations.
Ambrosone et al, 2006 (81) Germany	446	60 / 26-87	BED Mean 54 Gy ±4.8 Gy (35.5-64.5)	CTCAE v 2.0 modified	CTCAE < 2c (369)	CTCAE ≥ 2c (77)	*GSTA1* *GSTM1* *GSTP1* *GSTT1*		MALDI-TOF mass spectrometry and PCR	*GSTP1* GG genotype was associated with severe RD. When the model was adjusted for confounding factors, there was an increase in the hazard of toxicity among women with *GSTP1* GG genotype (adjusted HR: 2.28; 95% CI: 1.04–4.99), in comparison with women with common AA genotype. There were no associations noted for *GSTM1*, *GSTT1*, or *GSTA1*. When 'at-risk' alleles were combined, no cumulative effects were noted.
Borghini et al, 2014 (82) Italy	59	58/ 35-80	(40.05 – 50) + boost 10Gy	RTOG	RTOG 0 (35)	RTOG ≥ 1 (24)	*GSTM1* *GSTT1* *H2AX* *XRCC1* *XRCC3*	 rs8551 rs7350 rs25487 rs861539	PCR and PCR-RFLP	*GSTM1* distribution was significantly different between the groups (p = 0.02). The *GSTM1* null allele was associated with an increased acute RD (HR 2.4, 95% CI = 1.1–5.3, p = 0.04). The null *GSTM1* allele remained related to acute RD (HR 2.4, 95% CI = 1.1–5.5, p = 0.03) when controlled for BMI. The genotype distribution of other SNPs was not significantly different. The integrated effect of six SNPs, with the sum of the high-risk alleles, presented a genetic risk score significantly associated with the risk of early acute RD (HR: 1.37; 95% CI = 1.1–1.76; p < 0.01).
Chang-Claude et al, 2005 (83) Germany	446	60/ 26-87	BED Mean 54 Gy ±4.8 Gy (35.5-64.5)	CTCAE v 2.0 modified	CTCAE < 2c (369)	CTCAE ≥ 2c (77)	*APE1* *XPD* *XRCC1* 	rs1130409 rs1799793 rs1052559 rs1799782 rs25489 rs25487	PCR	We found no significant association between the genetic variants of *XRCC1*, *APE1*, and *XPD* and the development RD in multivariate analysis. Stratification in normal weight and overweight patients (BMI ≥ 25) also showed no statistical difference in the association between SNPs and the development of severe acute RD. Considering joint effects, the wild-type allele carriers in *APE1* rs1130409 and *XRCC1* rs25487 SNPs, in patients with normal weight, reduced the risk of severe acute RD (HR: 0.19; IC 95%: 0.06-0.56; p= 0,009) compared with homozygous carriers.

Córdoba et al, 2016 (84) Argentina	80	59/ 26-79	(50-50.4) +boost 12-18 Gy	RTOG	RTOG < 2 (48)	RTOG ≥ 2 (32)	*GSTA1* rs3957356 *GSTP1* rs1695 *NOS3* rs179998 *SOD2* rs4880	PCR-RFLP	Patients treated with neo-adjuvant CT (n=25) homozygous carriers of the *NOS3* SNP (rs179998) (OR: 9.8; 95% CI: 211.6 - 0.45; p=0.041) were at higher odds of developing severe acute RD. The results of univariate and multivariate analysis showed no significant association of the other SNPs with odds for the development of severe acute RD (p >0.05).
De Langhe et al, 2014 (85) Belgium	377	Hospital 1 Median 57.5/30-82 Hospital 2 Median 59/35-82	(40.05-50.0) + boost 10 Gy	CTCAE v3.0	CTCAE < 2 (157)	CTCAE ≥ 2 (220)	*LIG3* rs3744355 *LTHA4* rs7970524 *MLH1* rs1800734 *NDUFB6* rs12003093 *PHLDA3* rs3888929 *VDR* rs476065 *XRCC3* rs861539	PCR-RFLP	The univariate analysis showed that severe acute RD was associated with the GA genotype of *MLH1* rs1800734 SNP and multivariate analysis did not modify the association (OR: 0.492; 95%CI: No Informed; p= 0.008). None of the other SNPs had any effect on the risk of severe acute RD.
Lee et al, 2020 (86) United States	416	55/ 27.5-82.5	Mean 58.4 Gy (45-50) + boost 10-16 Gy	ONS	ONS <4 (301)	ONS ≥ 4 (115)	*ATM* rs61915066 *CHEK1* rs11220184 *LCP2* rs4867592 *RAD51C* rs405684 *TGFβ1* rs4803455 rs2241714 *ERCC2* rs60152947 rs10404465 rs1799786 + others 1960 SNPs in 48 genes were tested.	Illumina Human Omni 2.5-8 v1 genome-wide BeadChip array	In a multivariate analysis the frequency of minor allele/ major allele in *ATM* rs61915066 (OR= 2.64; 95% CI: 1.37-5.09; p= 0.004), *CHEK1* rs11220184 (OR= 1.69; 95% CI: 1.12-2.56; p= 0.013), *RAD51C* rs405684 (OR= 1.6; 95% CI: 1.14-2.27; p= 0.007), *TGFβ1* rs4803455 (OR= 1.50; 95% CI: 1.05-2.13; p= 0.025) and *ERCC2* rs1799786 (OR= 1.74; 95% CI: 1.16-2.59; p= 0.007) were significantly associated with increase severe acute RD. The SNP rs2241714 in *TGFβ1* (OR= 0.57; 95% CI: 0.38-0.83; p= 0.004), rs302877 in *RAD51C* (OR= 0.59; 95% CI: 0.40-0.86; p= 0.006), and the SNPs rs60152947 and rs10404465 in *ERCC2* (OR= 0.42; 95% CI: 0.23-0.79; p= 0.007 and OR= 0.59; 95% CI: 0.41-0.87; p= 0.007 respectively) were associated with decreased RD.

Mangoni et al, 2011 (87) Italy	87	NI	BED Mean 56.4 Gy ±4.8 Gy (44-50) + boost 10-16 Gy	CTCAE V 2.0 modified	CTCAE < 2c (79)	CTCAE ≥ 2c (8)	*GSTM1* *GSTT1* *MGMT* rs12917 *MLH1* rs1799977 *MSH2* rs2303428 *MSH3* rs26279 *XPD* rs1799793 rs1052559 *XRCC1* rs25487 rs1799782 *XRCC3* rs861539	PCR	The occurrence of acute RD was increased in carriers of the SNP rs861539 in *XRCC3* gene (HR: unquantifiably high), rs2303428 in *MSH2* gene (HR = 53.36; 95%CI: 3.56–798.98), and rs26279 in *MSH3* gene (HR unquantifiably high) considering either all patients or those receiving RT only. When considering joint effects for *XRCC1*, *XPD*, and for *GST* genes, compared with carriers of the wild-type alleles in both *XRCC1* SNPs, carriers of the wild-type *XRCC1*-399 Arg allele and the variant *XRCC1*- 194 Trp allele had a significant risk of radiosensitivity (HR: 38.26; 95%CI: 1.19–1232.52).
Mumbrekar et al, 2017 (88) India	126	Median 47/ 26-72	Median 50 Gy +boost 10 Gy	RTOG	RTOG < 2 (82)	RTOG ≥ 2 (44)	*ALAD* rs818707 *BAX* rs918546 *CD44* rs8193 *MAD2L2* rs2294638 *MAP3K7* rs3757244 *MAT1A* rs2282367 *NEIL3* rs3805169 *NFE2L2* rs1806649 *OGG1* rs2075747 *PTTG1* rs2961950 rs2961952 rs3811999 *RAD17* rs3756402 *RAD9A* rs2286620 *REV3L* rs240962	TaqMan SNP genotyping and PCR	Only the SNP rs8193 with CT genotypes (OR: 2.68; 95% CI: 1.13-6.35; p= 0.0232) and CT+TT (OR: 2.31; 95% CI: 1.02-5.23; p= 0.0422) in *CD44* gene were associated with the of severe acute RD. A 2-locus gene-gene interaction model after adjusting for clinical covariates suggested that the combination between *MAT1A* rs2282367, and *CD44* rs8193 is associate with severe acute RD.

							rs190246 *RPS6KB2* rs917570 *SH3GL1* rs243336 rs73234 *TGFβR3* rs1926261 *XRCC1* rs25487 *ZNF830* rs3744355		
Murray et al, 2011 (89) United Kingdom	480	NI	50 Gy/ NI	CTCAE v 3.0 modified	CTCAE < 2 (415)	CTCAE ≥ 3 (65)	*LIG3* rs3744355 rs1052536 rs3744357 *PTTG1* rs2910190 rs3811999 rs2961951 *RAD9A* rs2255990 rs2286620	ASO hybridization SNPlex™ Genotyping	The only SNP that shows an association with acute RD is the *LIG3* SNP rs3744355 (p = 0.0046). The results of the association analysis did not present. The linear regression test showed no significant effect on the association of *LIG3* and severe acute RD when adjusted for radiation dose or breast size. A haplotype analysis using the three *LIG3* SNPs shows no association.
Popanda et al, 2006 (90) Germany	446	60 / 26-87	BED Mean 54 Gy ±4.8 Gy (35.5-64.5)	CTCAE v 2.0 modified	CTCAE < 2c (369)	CTCAE ≥ 2c (77)	*NBS1* rs1805794 *XRCC2* rs3218536 *XRCC3* rs861539	PCR-RFLP and Fluorescence-based melting curve analysis	The study did not obtain a significant association between the genetic SNPs in *NBS1*, *ERCC2* and *XRCC3* genes and the severe acute RD. There was no statistically significant association between SNPs and severe acute RD when patients were stratified into normal weight or overweight. There was also no statistically significant difference when allele-pooled effects were examined.
Raabe et al, 2012 (91) Germany	83	60/ 36–80	50-50.4 Gy + boost 9-10 Gy	RTOG	RTOG < 2 (37)	RTOG ≥ 2 (46)	*ATM* rs1501516 *GSTP1* rs1695 *SOD2* rs4880 *TGFβ1* rs1800469 *XPD* rs13181 *XRCC1* rs25487	PCR-RFLP and MALDI-TOF	They had no statistically significant association between erythema and SNPs. In further analysis, small breast volume revealed a significant allele-dose dependent association for SNP rs1800469 in *TGFβ1* (OR: 3.10, 95% CI: 1.11–10.21, p = 0.028), and patients with larger breast volume had a significant association for SNP rs13181 in *XPD* (OR = 3.95, 95% CI: 0.91–22.75, p = 0.046). However, a value of 1 is included in the 95% confidence interval. No significant association was found for any of the other four SNPs.

Suga et al, 2007 (92) Japan	399	Lower RD 54/ 26-88 Severe RD 50/ 30-77	Lower RD Mean 49.97 Gy (46-60) Severe RD Mean 49.87 Gy (46-50)	CTCAE v2.0	CTCAE < 2 (290)	CTCAE ≥ 2 (109)	*ALAD* rs818707 *BAX* rs918546 *CD44* rs8193 *COMT* rs3087869 *LIG3* rs3744355 *MAD2L2* rs2294638 *MAP3K7* rs3757244 *MAT1A* rs2282367 *NEIL3* rs3805169 *NFE2L2* rs1806649 *OGG1* rs2075747 *PTTG1* rs3811999 rs2961950 rs2961952 *RAD17* rs3756402 *RAD9A* rs2286620 rs917570 *REV3L* rs190246 rs240962 *SH3GL1* rs73234 rs243336 *TGFβ3* rs2268622 *TGFβR3* rs913060 rs1926261 *XRCC1* rs25487 + others 485 SNPs in 104 genes were tested	PCR and MassARRAY W system (Sequenom, USA)	In the genotype frequency analysis 21 SNPs in 17 genes showed an association with severe RD in dominant or recessive model, being: *MAD2L2* rs2294638 Recessive Model - OR: 1.87; 95%IC: 1.18-2.97; p= 0.0087 *MAP3K7* rs3757244 Recessive Model - OR: 2.40; 95%IC: 1.15-7.54; p= 0.038 *MAT1A* rs2282367 Recessive Model - OR: 2.04; 95%IC: 1.09-4.67; p= 0.047 *NEIL3* rs3805169 Dominant Model - OR: 0.19; 95%IC: 0.04-0.59; p= 0.0036 *OGG1* rs2075747 Dominant Model - OR: 3.15; 95%IC: 1.38-13.92; p= 0.017 *PTTG1* rs3811999 Recessive Model OR: 1.92; 95%IC: 1.15-3.46; p= 0.018 *PTTG1* rs2961950 Recessive Model OR: 1.62; 95%IC: 1.04-2.54; p= 0.033 *PTTG1* rs2961952 Recessive Model OR: 0.61; 95%IC: 0.37-0.95; p= 0.040 *RAD17* rs3756402 Recessive Model OR: 1.83; 95%IC: 1.07-3.51; p= 0.036 *RAD9A* rs2286620 Recessive Model OR: 1.85; 95%IC: 1.17-3.04; p= 0.012 *REV3L* rs190246 Dominant Model - OR: 0.50; 95%IC: 0.29-0.88; p= 0.016 *REV3L* rs240962 Recessive Model OR: 0.56; 95%IC: 0.32-0.92; p= 0.028 *SH3GL1* rs73234 Recessive Model OR: 0.60; 95%IC: 0.37-0.95; p= 0.030 *SH3GL1* rs243336 Recessive Model OR: 0.56; 95%IC: 0.34-0.89; p= 0.016 *XRCC1* rs25487 Dominant Model - OR: 0.37; 95%IC: 0.17-0.84; p= 0.015 In the *CD44* gene, the GGTT haplotype significantly increased the RD compared to the most common GGTC haplotype (OR: 2.17; 95% CI: 1.07–4.43). The CG haplotypes in *MAD2L2* (OR: 0.55; 95% CI: 0.35-0.87), GTTG in *PTTG1* (OR: 0.48; 95% CI: 0.24-0.96), TCC (OR: 0.48; 95% CI: 0.26-0.89) and CCG (OR: 0.50; 95% CI: 0.27-0.92) in *RAD9A* and GCT in *LIG3* (OR: 0.46; 95% CI: 0.22-0.93) were associated with a reduction in RD compared to the most common haplotype at each locus.

Tan et al, 2006 (93) Germany	446	60 / 26-87	BED Mean 54 Gy ±4.8 Gy (35.5-64.5)	CTCAE v 2.0 modified	CTCAE < 2c (369)	CTCAE ≥ 2c (77)	*TP53* *P21*	p53PIN3 rs1042522 rs1801270	PCR and Fluorescence-based melting curve	The study did not observe a significant association between *TP53* and *p21* SNPs and the risk of severe acute RD. Further analysis for patients with normal weight/overweight were not statistically significant in the association between SNPs and the risk of severe acute RD. Analyzes by non-attenuating weight stratification statistically significant p-value.
Terrazzino et al, 2012 (94) Italy	286	60.8/ NI	50–50.4 Gy + boost 9–16 Gy	RTOG	RTOG < 2 (197)	RTOG ≥ 2 (89)	*eNOS* *GSTA1* *GSTP1* *MSH2* *MSH3* *SOD2* *TGFβ1* *TP53* *XPD* *XRCC1*	rs1799983 rs3957356 rs1695 rs2303428 rs26279 rs4880 rs1800469 rs1982073 rs1042522 rs1052559 rs3213235 rs1799782 rs25487	PCR-RFLP	Univariate logistic regression analysis revealed an association between homozygous carriers of the eNOS T allele (OR: 2.042, 95% CI: 1.047–3.982; p= 0.036) and severe acute RD. Results of the multivariable logistic regressions analysis showed a significant association of *XRCC1* T-rs3213235 (OR: 2.240, 95% CI: 1.015–4.941; p = 0.046) and *eNOS* rs1799983 SNPs (OR: 2.473, 95% CI: 1.220–5.012; p = 0.012) with the risk of severe acute RD. None of the other SNPs investigated were found related in the univariate logistic regression and multivariable analysis to severe acute RD. Patients that had 2 at-risk genotypes were more likely to develop acute radiosensitivity compared to patients with 1 at-risk genotype (OR: 2.663, 95% CI: 1.237-5.732, p= 0.012) or for patients with at-risk genotype 0 (OR: 5.44, 95% CI: 1.858–15.910, p= 0.002).
Zhou et al, 2010 (95) China	119	Median 47/ 26-73	Median 50.2 Gy (46-54)	CTCAE v3.0	CTCAE < 2 (50)	CTCAE ≥ 2 (69)	*XRCC1*	rs3213245 rs1799782 rs25489 rs25487	PCR-RFLP	The patients -77TC carriers in *XRCC1* rs3213245 SNP had a significantly increased of severe acute RD (OR: 3.66; 95% CI: 1.04–17.95; p=0.033) compared with the -77TT carriers. Patients with *XRCC1* -77TC and CC genotypes had a significantly increased severe acute RD (OR: 3.88; 95% CI: 1.14–14.77; p=0.016) compared with the -77TT carriers. There was no statistically significant association between the *XRCC1* rs1799782, rs25489 and rs25487 SNPs and severe acute RD. However, this SNP deviated from the Hardy-Weinberg Equilibrium.

ASO: Allele Specific Oligonucleotide; BED: Biologically Effective Radiotherapy Dose; BMI: Body Mass Index; CI: Confidence Interval; CTCAE: Common Terminology Criteria for Adverse Effects; Gy: Gray; HR: Hazard Ratio; MALDI-TOF: matrix-assisted laser desorption/ionization time-offlight; NI: No informed; ONS: Oncology Nursing Society; OR: Odds Ratio; PCR: Polymerase Chain Reaction; PCR-RFLP: Polymerase Chain Reaction – Restriction Fragment Length Polymorphism; RD: Radiodermatitis; RT: Radiotherapy; RTOG: Radiation Therapy Oncology Group; SNPs: Single Nucleotide Polymorphisms.

Gene: *ALAD: aminolevulinate dehydratase; APE1: acclimation of photosynthesis to environment; ATM: ATM serine/threonine kinase; BAX: BCL2 associated X, apoptosis regulator; CAT: catalase; CD44: CD44 molecule; CHEK1: checkpoint kinase 1; COMT: catechol-O-methyltransferase; eNOS: endothelial nitric oxide synthase; ERCC2: ERCC excision repair 2, TFIIH core complex helicase subunit; GSTA1: glutathione S-transferase alpha 1; GSTM1: glutathione S-transferase mu 1; GSTP1: glutathione S-transferase pi 1; GSTT1: glutathione S-transferase theta 1; H2AX: H2A.X variant histone; LCP2: lymphocyte cytosolic protein 2; LIG3: DNA ligase 3; LTHA4: leukotriene A-4 hydrolase; MAD2L2: mitotic arrest deficient 2 like 2; MAP3K7: mitogen-activated protein kinase kinase kinase 7; MAT1A: methionine adenosyltransferase 1ª; MGMT: O-6-methylguanine-DNA methyltransferase; MLH1: mutL homolog 1; MnSOD: manganese superoxide dismutase; MPO: myeloperoxidase; MSH2: mutS homolog 2; MSH3: mutS homolog 3; NBS1: nijmegen breakage syndrome 1; NDUFB6: NADH:ubiquinone oxidoreductase subunit B6; NEIL3: nei like DNA glycosylase 3 ; NFE2L2: nuclear factor, erythroid 2 like 2; NOS3: nitric oxide synthase 3; OGG1: 8-oxoguanine DNA glycosylase ; P21: p21 protein regulates cell cycle; PHLDA3: pleckstrin homology like domain family A member 3; PTTG1: PTTG1 regulator of sister chromatid separation, securin; RAD17: RAD17 checkpoint clamp loader componente; RAD51C: RAD51 paralog C; RAD9A: RAD9 checkpoint clamp component A; REV3L: REV3 like, DNA directed polymerase zeta catalytic subunit; RPS6KB2: ribosomal protein S6 kinase B2; SH3GL1: SH3 domain containing GRB2 like 1, endophilin A2; SOD2: superoxide dismutase 2; TGFβ3: transforming growth factor beta 3; TGFβR3: transforming growth factor beta receptor 3; TGFβ1: transforming growth factor beta 1; TP53: tumor protein p53; VDR: vitamin D receptor; XPD: Xeroderma pigmentosum D; XRCC1: X-ray repair cross complementing 1; XRCC2: X-ray repair cross complementing 2 ;XRCC3: X-ray repair cross complementing 3; ZNF830: zinc finger protein 830.*

5.4.3. Risk of Bias in Studies

Most studies had low risk of bias (n = 13; 81%). Three studies presented moderate risk of bias (87-89) mainly for not making clear the presentation of some data. Details on the judgment of risk of bias are provided in Table 2, and justifications for the judgment of items in each article are provided in Appendix 3. All studies were evaluated with low risk of bias only for items that assess methods of measuring exposure and outcome, time of follow-up of the sample to assess the outcome, and description of the reasons for the loss of patients in the sample. Some articles reported that there were losses of patients in the study, but they justify that it was due to problems with the blood sample collected for analysis of the SNPs. Therefore, they had low risk of bias in this item.

Table 2 – Risk of Bias of individual cohort studies

Study	Assessment criteria*											Total	Risk of bias
	Q01	Q02	Q03	Q04	Q05	Q06	Q07	Q08	Q09	Q10	Q11		
Ahn et al, 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	Low
Ambrosone et al, 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	Low
Borghini et al, 2014	N	Y	Y	U	U	Y	Y	Y	Y	NA	Y	70%	Low
Chang-Claude et al, 2005	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	Low
Córdoba et al, 2016	Y	Y	Y	Y	U	Y	Y	Y	Y	NA	Y	90%	Low
De Langhe et al, 2014	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	100%	Low
Lee et al, 2020	Y	Y	Y	Y	Y	Y	Y	Y	Y	NA	Y	100%	Low
Mangoni et al, 2011	U	Y	Y	U	U	Y	Y	Y	Y	U	U	55%	Moderate
Mumbrekar et al, 2017	Y	Y	Y	U	U	U	Y	Y	U	U	Y	55%	Moderate
Murray et al, 2011	U	Y	Y	U	U	Y	Y	Y	Y	U	U	55%	Moderate
Popanda et al, 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	91%	Low
Raabe et al, 2012	Y	Y	Y	N	U	U	Y	Y	Y	NA	Y	70%	Low
Suga et al, 2007	Y	Y	Y	U	U	U	Y	Y	Y	NA	Y	70%	Low
Tan et al, 2006	Y	Y	Y	Y	Y	Y	Y	Y	Y	U	Y	91%	Low
Terrazzino et al, 2012	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	100%	Low
Zhou et al, 2010	Y	Y	Y	U	U	Y	Y	Y	Y	U	Y	73%	Low

*Assessment according to Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cohort Studies: Q1 - Were the two groups similar and recruited from the same population?; Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?; Q3 - Was the exposure measured in a valid and reliable way?; Q4 - Were confounding factors identified?; Q5 - Were strategies to deal with confounding factors stated?; Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?; Q7 - Were the outcomes measured in a valid and reliable way?; Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?; Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?; Q10 - Were strategies to address incomplete follow up utilized?; Q11- Was appropriate statistical analysis used?. Legend: Y= Yes; N= No; U= Unclear; NA= Not Applicable. Total= ΣY Applicable Items (the Not Applicable (NA) items were excluded from the sum). Risk of bias was categorized as high when the study reaches up to 49% score “yes”, moderate when the study reached 50% to 69% score “yes”, and low when the study reached more than 70% score “yes”.

5.4.4. Results of Individual Studies

Ahn et al (2006) (80) evaluated SNPs in the *CAT, eNOS, MnSOD* and *MPO* genes, and Ambrosone et al (2006) (81) evaluated SNPs in the *GSTA1, GSTM1, GSTP1,* and *GSTT1* genes, but both did not specify which polymorphisms were evaluated. However, the women with body mass index ≥ 25 (overweight/obese) presented association between *eNOS* GG genotypes and severe acute RD (HR: 6.39; 95% CI: 2.53-16.15) or *MPO* GG genotypes and severe acute RD (HR: 3.61; 95% CI: 1.78-7.35) (Ahn et al, 2006). In Ambrosone et al (2006), women with *GSTP1* GG genotype presented more severe RD (adjusted HR: 2.28; 95% CI: 1.04–4.99), than women with common AA genotype.

Suga et al (2007) (92) selected 137 candidate genes for genotyping 1,025 SNPs in these genes. However, 515 SNPs were removed from the analysis because they had low sensitivity of allele distinction, or were not polymorphic in the sample, or had an allelic frequency <0.5%, or were triallelic SNPs, or did not obey the Hardy-Weinberg Equilibrium (HWE), or the genotypes were equal to contiguous SNPs. Finally, only 510 SNPs in 123 genes were analyzed for association with severe RD (92). However, in the article, the authors present only the SNPs that had a statistically significant association, individualized or in haplotype blocks with severe RD, which were described in table 1 of this review.

Lee et al (2020) (86) selected 53 genes that are already known to participate in DNA damage repair pathways and evaluated the association of 1,968 SNPs in these genes with severe RD. The number of SNPs evaluated for each gene is presented in the article. The study found an association between SNPs in the *ATM, CHEK1, ERCC2, RAD51C,* and *TGFβ1* genes and the development of severe RD according to the presence of minor or major allele, as shown in table 1 of this review. The article did not present any association data for the other SNPs that were evaluated.

Regarding ethnicity, 6 studies included Caucasian patients (80,81,83,89,90,93) and 5 studies are composed of the same sample with analysis of SNPs in different genes (80,81,83,90,93). In Lee et al (2020) (86), the sample was composed of Hispanic whites, blacks or African Americans, non-Hispanic whites, and others. In Murray et al (2011) (89), some patients were of British, Indian, or Pakistani descent, from other

European, African, Caribbean, and Chinese countries. The other articles included in this review (82,84,85,88,91,92,94,95) did not inform the ethnicity of the included patients.

Regarding the HWE test, two studies did not report if they tested for the SNPs evaluated (80,81). Borghini et al (2014) (82) tested for the HWE but did not report if all SNPs complied with the parameters of the distribution of genotypes. Other studies had all genotypic distributions in HWE (83,84,89,90,93,94). Lee et al (2020) (86) and Suga et al (2007) (92) excluded from the analysis all those SNPs that did not comply with the HWE, but they did not report which SNPs were excluded.

The following SNPs were not consistent with the HWE and were excluded from the analyzes of association with severe RD: De Langhe et al (2014) (85) excluded the SNP rs4867592 in the *LCP2* gene from the analyses, Mumbrekar et al (2017) (88) excluded from the analyzes five SNPs (rs818707 in *ALAD*, rs3757244 in *MAP3K7*, rs1806649 in *NFE2L2*, rs3756402 in *RAD17*, and rs2286620 in *RAD9A* gene) and Raabe et al (2012) (91) excluded from the analysis the SNP rs4880 in the *SOD2* gene. Although in Zhou et al (2010) (95) the rs3213245 and rs25489 SNPs in the *XRCC1* gene and in Mangoni et al (2011) (87) the rs1799793 SNP in the *XPD* gene and the rs1799977 SNP in the *MLH1* gene were not consistent with HWE, they were not excluded from the analyzes of association with severe RD.

There are many genes and SNPs being evaluated in the studies included in this review. However, not all genes were evaluated for the same SNPs. Figure 2A summarizes the genes and Figure 2B shows the SNPs that were evaluated in more than one study included in this review.

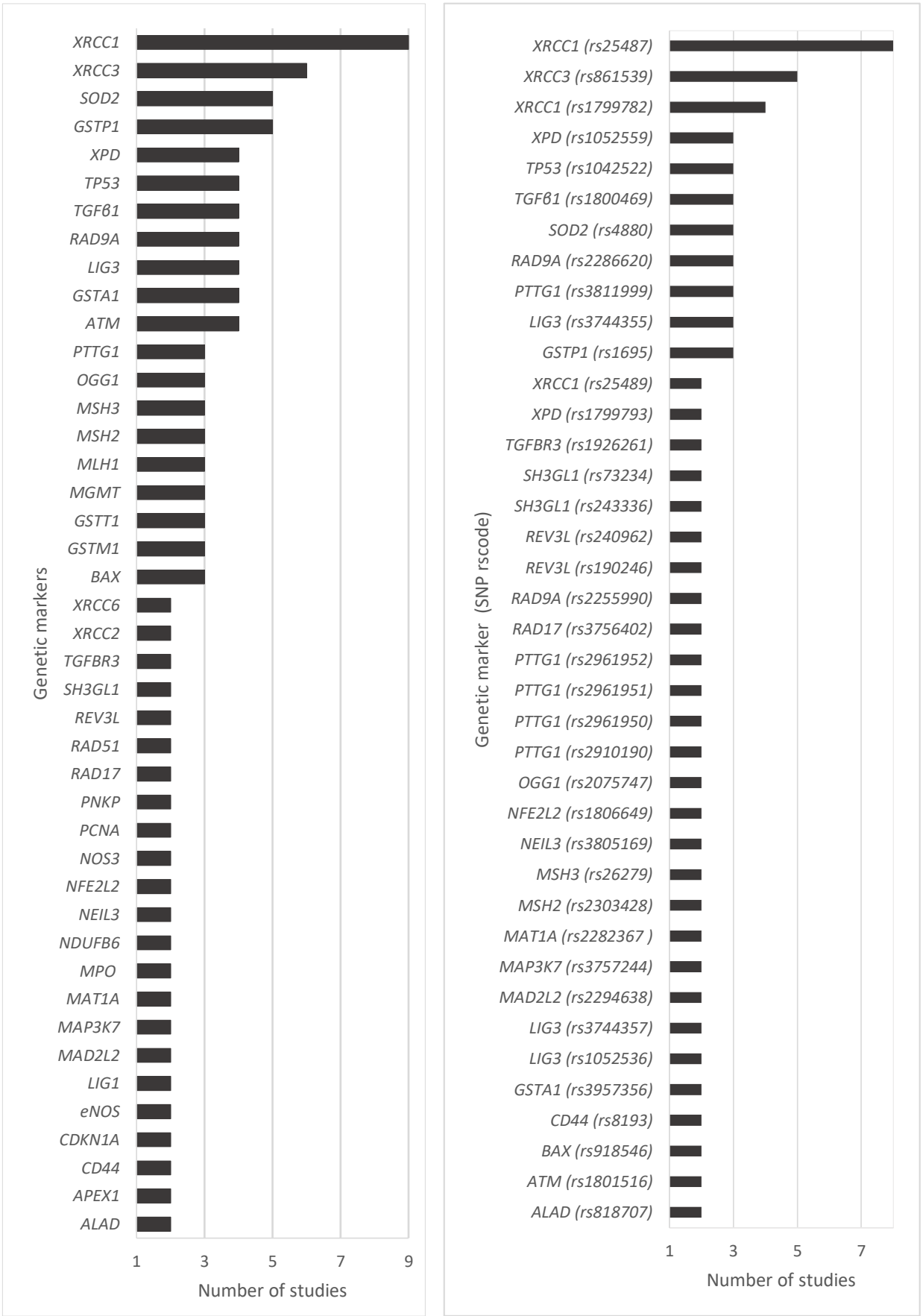


Figure 2 – Frequency of evaluation of genetic markers in the studies included in this review: A) Genes; B) rs code for the Single nucleotide polymorphisms.

Details on the main results that present the association between SNPs and the development of severe RD can be found in Table 1.

The only SNPs that were associated with RD in more than one study were rs8193 in the *CD44* gene and rs3744355 in the *LIG3* gene (88,89,92). However, the results are controversial. The CT and CT+TT genotypes for the rs8193 SNP in the *CD44* gene were associated with increased severe RD in the Mumbrekar et al (2017) (88) study (OR: 2.68; 95% CI: 1.13-6.35; p= 0.0232 and OR: 2.31; 95% CI: 1.02 -5.23; p= 0.0422), while in Suga et al (2007) (92) the recessive model was associated with a decrease in severe RD (OR: 0.48; 95%CI: 0.28-0.76; p= 0.0034).

Regarding the rs3744355 SNP in the *LIG3* gene, Murray et al (2011) (89) found an association with the occurrence of RD, and although there was significance (p = 0.0046) the authors did not report whether it was an increase or a decrease in severity, while Suga et al (2007) (92) found association of the dominant model of this gene with severe RD decrease (OR: 0.32; 95%CI: 0.13-0.73; p= 0.006). Zhou et al (2010) (95) found an association between SNP that did not follow HWE and therefore was not considered.

Haplotype analysis was performed on 11 studies included in this review (80-83,87-90,92-94). However, only 6 of them found a statistically significant association (80,82,87,92-94). Association details can be accessed from the main results in Table 1.

5.4.5. Results of syntheses

SNPs that were evaluated in more than one study were eligible for inclusion in the meta-analysis, if they had frequency data available. Data of the rs3213245 and rs25489 SNPs in the *XRCC1* gene, evaluated in Zhou et al (2010) (95), and of the rs1799793 SNPs in the *XPD* gene of the article by Mangoni et al (2011) (87), were excluded from the meta-analysis because they were not consistent with the HWE.

5.4.5.1. Prevalence of the SNPs in patients that present RD

For prevalence meta-analysis 10 studies (82-84,88,90-95) were included as they had frequency data on patients who presented any grade of RD and had SNPs. Figure 3 presents general, data on the prevalence of all evaluated SNPs. For more details, see Appendix 4. The random effects model was used for meta-analysis of all SNPs, considering that there was intrinsic heterogeneity in the samples as they were from different locations.

Overall, data were available to assess the prevalence of 22 SNPs included in this review for breast cancer patients who presented RD, as follows: nine of these SNPs occur in genes that participate in cell cycle regulation (*CD44* rs8193; *REV3L* rs190246; *PTTG1* rs3811999 ; *PTTG1* rs2961952; *PTTG1* rs2961950; *MAD2L2* rs2294638; *BAX* rs918546; *SH3GL1* rs73234; *SH3GL1* rs243336); four SNPs occurred in genes that participate in DNA damage repair pathways by base excision (*XRCC1* rs1799782; *XRCC1* rs25487; *XPD* rs1052559; *NEIL3* rs3805169); one SNP is involved in double-stranded break repair (*XRCC3* rs861539), and another SNP is involved in double-stranded break signal transduction (*TP53* rs1042522); four SNPs are involved in the reactive oxygen species pathway and oxidative stress (*OGG1* rs2075747; *GSTP1* rs1695; *SOD2* rs4880; *GSTA1* rs3957356); *TGFB1* (rs1800469) and *TGFβR3* (rs1926261) are profibrotic and inflammatory cytokine; and *MAT1A* (rs2282367) which participates in other pathways.

The most prevalent SNP was rs1800469 in the *TGFβ1* gene (41%; 95%CI: 23-60). The second most prevalent SNP were rs3957356 in the *GSTA1* gene (36%; 95%CI: 24-48). All SNPs evaluated had a prevalence equal to or greater than 24%. However, all SNPs showed significant heterogeneity (p = 0) between studies, and the real effect variance between studies was 0.071 (SNP rs4880 in *SOD2* gene) to 0.988 (SNP rs1799782 in *XRCC1* gene). In addition, the inconsistency (I^2) was greater than 90% in all meta-analyses, indicating that more than 90% of the variability found in the studies is a product of the real variability of the population.

Because most SNPs were evaluated in only one study per country, meta-analysis of SNP prevalence by geographic region was not performed.

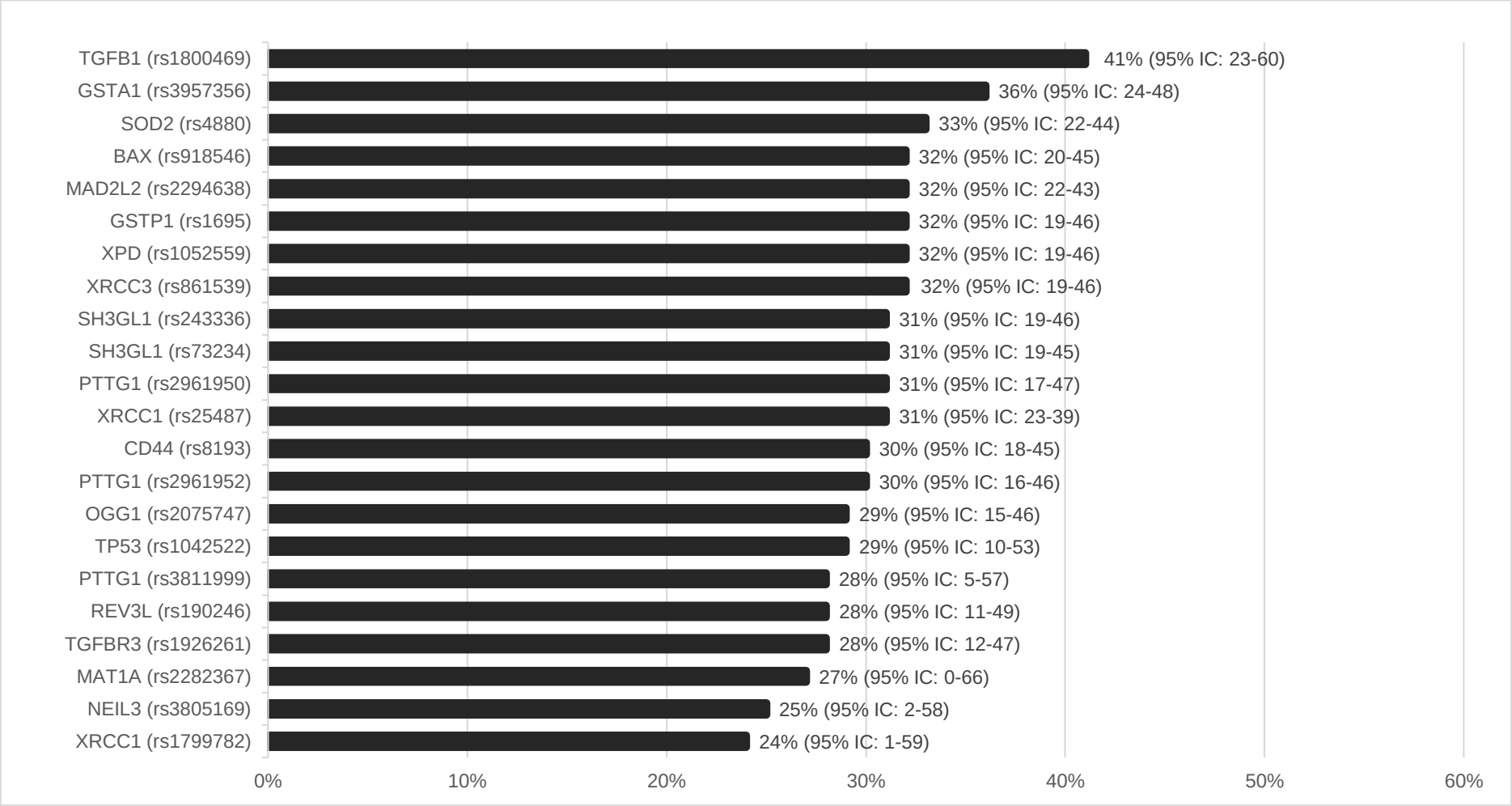


Figure 3 – Prevalence of the Single Nucleotide Polymorphisms in breast cancer patients that present radiation dermatitis.

5.4.5.2. Association between SNPs and severity of the RD

Among the studies that were included in the prevalence meta-analysis (82-84,88,90-95) two were excluded from the meta-analysis of association with RD severity (82,91). Here we consider as severe RD any manifestation of moist desquamation. Borghini et al (2014) (82) was excluded from the association meta-analysis because they considered severe RD manifestations of dry desquamation (RTOG grade 1). Raabe et al (2012) (91) was excluded from the association meta-analysis because they present data on erythema severity rather than signs of RD in general.

Association meta-analysis were performed for each SNP by genotype subgroup (homozygous for wild-type allele, homozygous for variant allele, and heterozygous). The only SNP that was included in the prevalence meta-analysis but excluded from the association meta-analysis was rs1800469 in the *TGFβ1* gene. This was because one of the studies that presented data for this SNP (91) considered severe RD manifestations of dry desquamation, which for the other studies included in the association meta-analysis considered as a lower manifestation of RD.

Among the genotypes associated with severe RD there was:

Wild homozygote: CC genotype of SNP rs3811999 in *PTTG1* gene (OR: 1.75 95% CI: 1.13-2.70; p=0.01); AA genotype of SNP rs2961950 in *PTTG1* gene (OR: 1.56; 95% CI: 1.4-2.34; p=0.03); GG genotype of SNP rs2294638 in *MAD2L2* gene (OR: 1.86 95% CI: 1.24-2.78; p=0.003); GG genotype of SNP rs2282367 in the *MAT1A* gene (OR: 2.03 95% CI: 1.18-3.48; p=0.01) (figure 4).

Heterozygous: CT genotype of SNP rs3957356 in *GSTA1* gene (OR: 5.57 95% CI: 1.73-17.87; p=0.004); CT genotype of SNP rs8193 in the *CD44* gene (OR: 1.79; 95% CI: 1.22-2.63; p=0.003); GC genotype of SNP rs243336 in *SH3GL1* gene (OR: 1.58; 95% CI: 1.08-2.31; p=0.02) (figure 4).

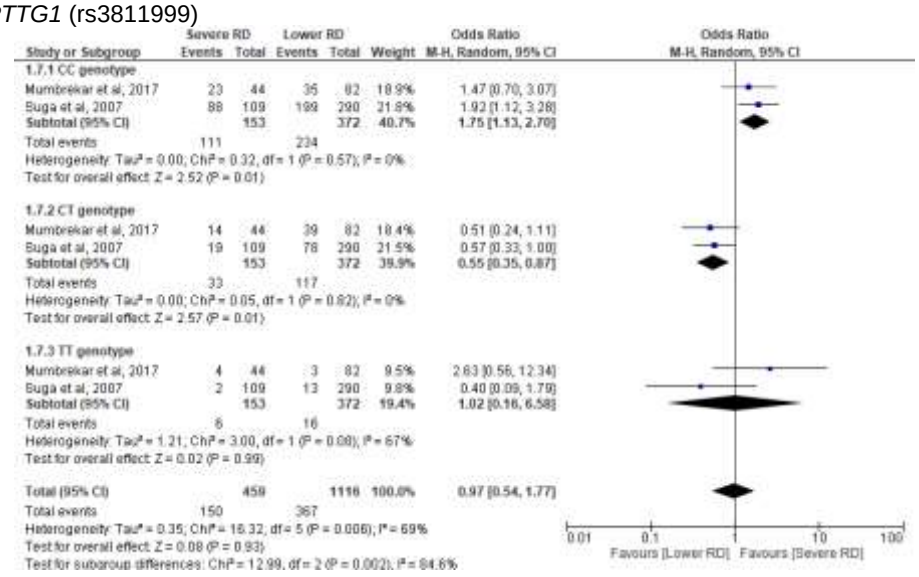
Among the genotypes associated with lower RD there was:

Wild homozygote: GG genotype of SNP rs2961952 in *PTTG1* gene (OR: 0.61; 95% CI:0.41-0.91; p=0.02); CC genotype of SNP rs8193 in the *CD44* gene (OR: 0.47; 95% CI:0.31-0.71; p=0.0004) (figure 4).

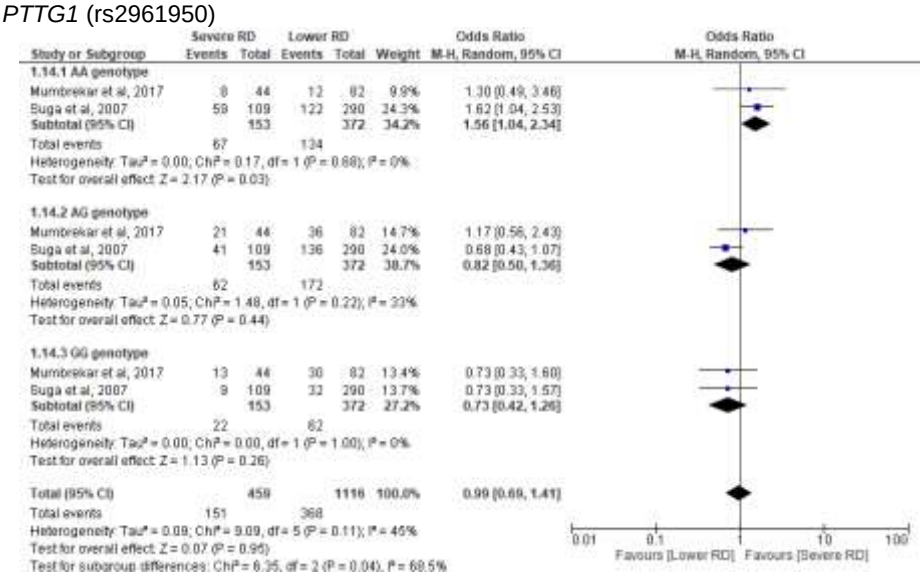
Heterozygous: CT genotype of SNP rs3811999 in *PTTG1* gene (OR: 0.55; 95% CI:0.35-0.87; p=0.01); GA SNP genotype rs2282367 in the *MAT1A* gene (OR: 0.49; 95% CI:0.27-0.87; p=0.01) (figure 4).

Variant homozygote: AA genotype of SNP rs2075747 in the *OGG1* gene (OR: 0.43; 95% CI: 0.19-0.99; p=0.05) (figure 4).

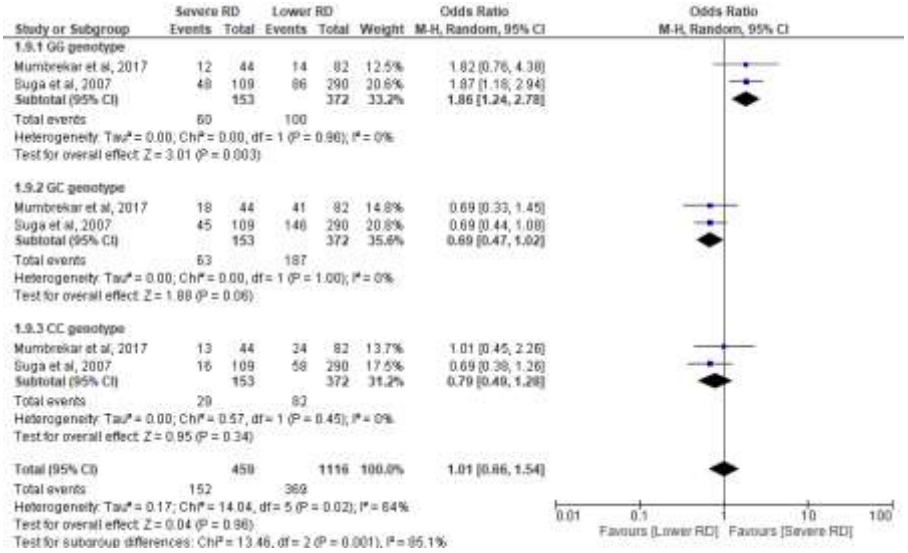
PTTG1 (rs3811999)



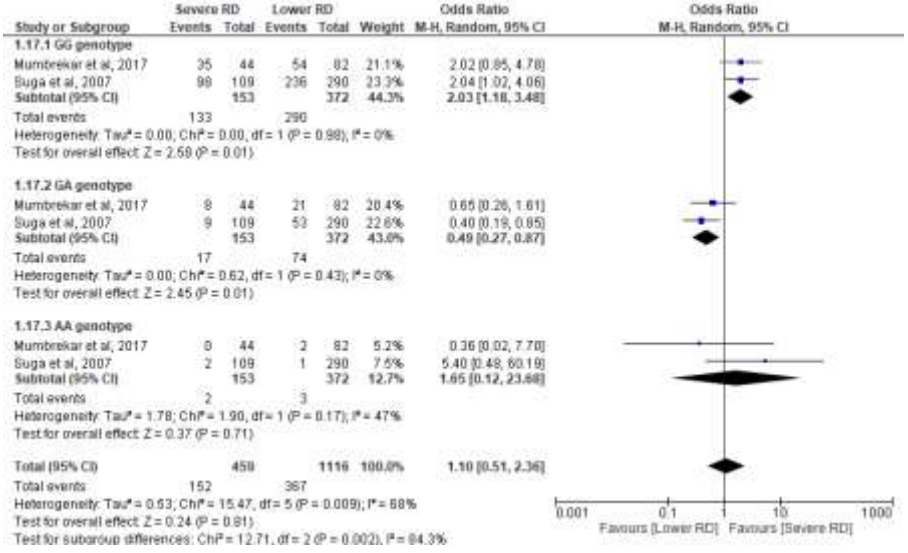
PTTG1 (rs2961950)



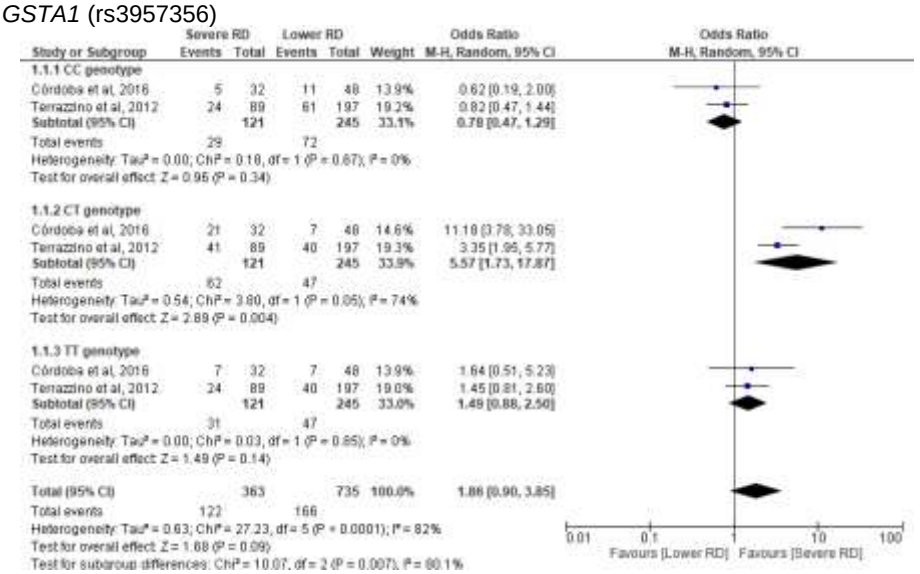
MAD2L2 (rs2294638)



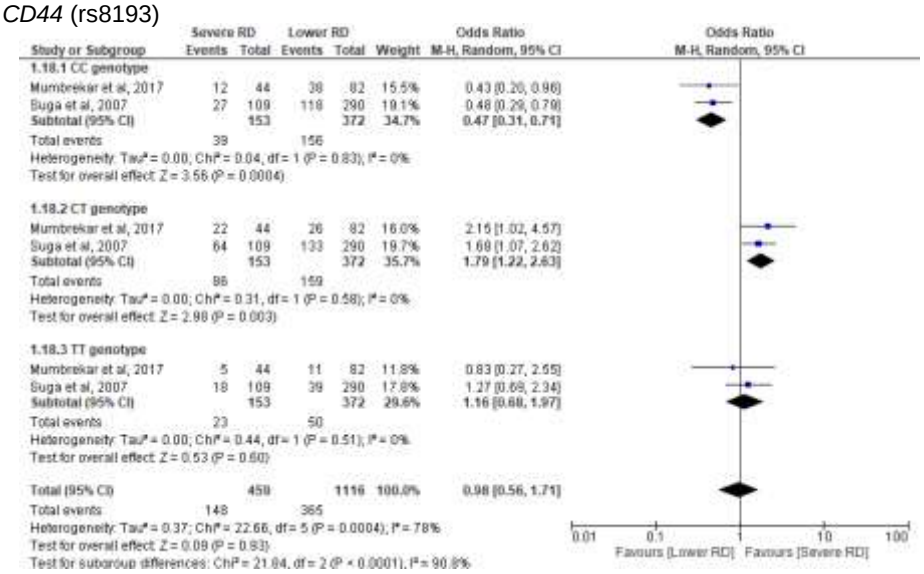
MAT1A (rs2282367)



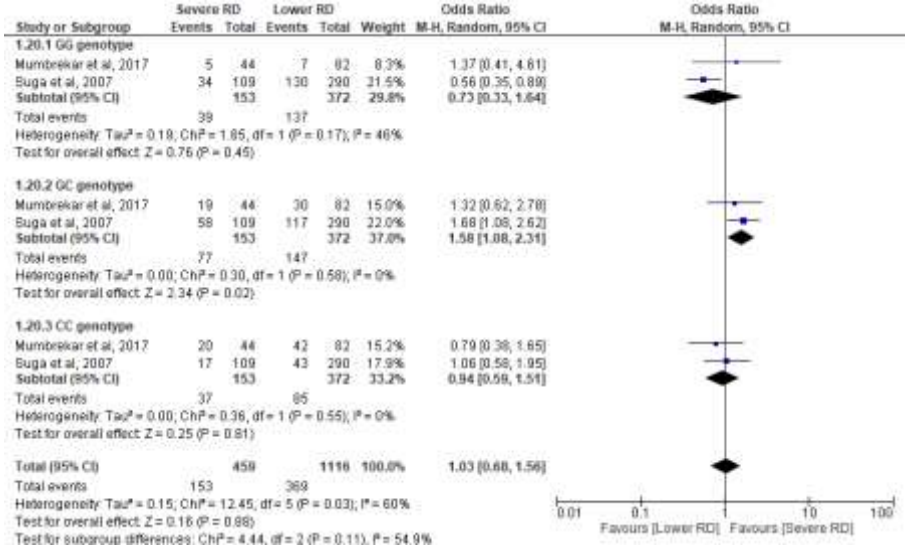
GSTA1 (rs3957356)



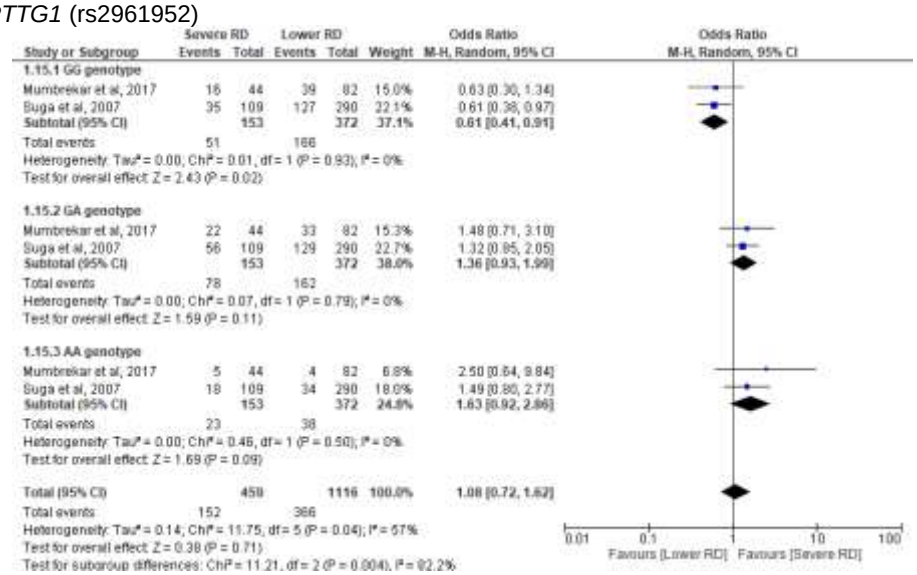
CD44 (rs8193)



SH3GL1 (rs243336)



PTTG1 (rs2961952)



OGG1 (rs2075747)

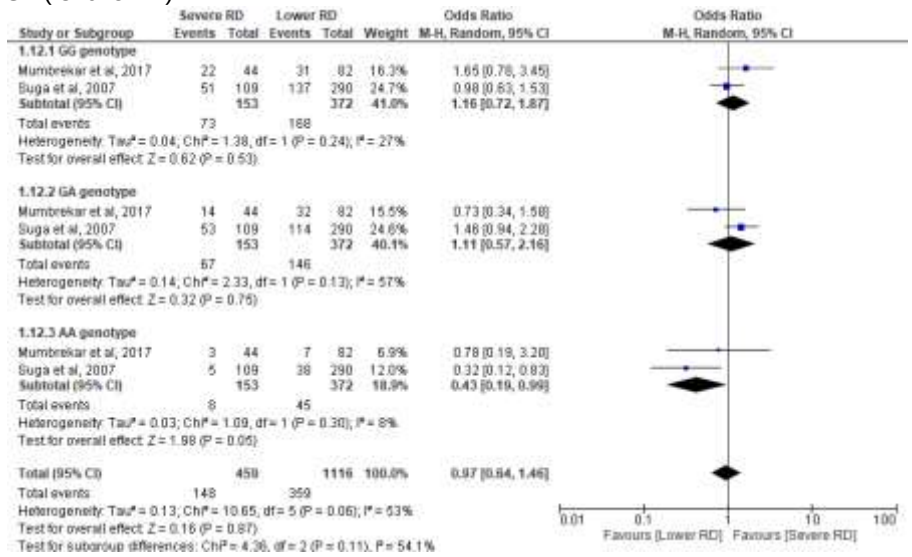


Figure 4 – Association meta-analysis of the SNPs and RD severity with statistical significance.

Association meta-analyses that were not statistically significant between other SNPs and RD severity can be accessed in Appendix 5.

5.4.6. Certainty of Evidence

Among the SNPs that had a significant association with RD severity, the CT genotype of SNP rs3957356 in the *GSTA1* gene, and the GG genotype of SNP rs2282367 in the *MAT1A* gene had low certainty of evidence in the evaluation by the GRADE system. For *GSTA1* genotype, although this genotype had a very large effect (OR: 5.57), the confidence interval was very wide (95%CI: 1.17-17.87) and there was significant heterogeneity (I^2:74%; p=0.05). The GG genotype of SNP rs2282367 in the *MAT1A* gene had a large effect (OR: 2.03; 95%CI: 1.18-3.48) and did not show statistically significant heterogeneity (I^2: 0%; p=0.98). All other SNPs that were or were not associated with RD severity had very low certainty of evidence in the GRADE system evaluation. The funding obtained in the studies was not considered as publication bias, because they were funded by scholarship programs, and none were companies. Details on the assessment of certainty of evidence for all SNPs evaluated in the association meta-analysis were reported in Appendix 6.

5.5. DISCUSSION

Acute radiation dermatitis is a very common adverse effect in breast cancer patients and has an important impact on quality of life (96,97). The literature already reports risk factors for RD. However, over the years, studies have shown that genetic variants could make individuals more radiosensitive. Thus, studies were developed to assess the potential of genetic variants to be responsible for predisposing to RD in cancer patients undergoing RT (5).

This is the first systematic review that assesses the potential of general SNPs to predict the occurrence or severity of acute RD in breast cancer patients. Other systematic reviews have already been done to assess the potential of specific SNPs to be associated with acute or late RD in breast cancer patients (71-73), but none have evaluated all the SNPs that have already been described in this population.

Among the main characteristics of the studies included in this review, the one that most varied among them was the RD scale of the measurement. However, most of them considered that the degree of severe RD would be determined by any manifestation of moist desquamation.

In individual studies, 29 SNPs had statistical significance in the association analysis with severe RD, indicating that they may increase the susceptibility of breast cancer patients undergoing RT to develop RD. Additionally, 15 SNPs were associated with a decreased susceptibility of the ocurrence of severe RD, and that is, it would be a protective factor for severe RD. However, most of these SNPs were statistically associated with RD in only one study. Only the rs8193 SNPs in the *CD44* gene and the rs3744355 SNP in the *LIG3* gene were associated with RD in breast cancer patients in more than one study included in this review. However, the results are controversial.

For the rs8193 SNP in the *CD44* gene, a study found an association between CT and CT+TT genotypes as a factor that increases the susceptibility of severe RD (88). On the other hand, another study found association of the rs8193 SNP in the *CD44* gene, as a factor that decreases the susceptibility of severe RD (92).

The human *CD44* gene is a transmembrane cell adhesion glycoprotein that emits signals for cell mobility, maintenance, survival, and the ability to invade normal and tumor cells (98-102). Despite being expressed in almost all dermis cells, the mechanism of action of this gene in wound healing is not known (103). A case-control study reported that the C allele of SNP rs8193 was related to the risk of gastric cancer (99). Lin et al (2018) (102) describe those other studies have shown that SNPs in the *CD44* gene are present in 84% of breast cancer patients. However, there are still no studies associating the rs8193 SNP and breast cancer. The prevalence of the rs8193 SNP in the *CD44* gene in this review was 30%. The CC genotype was associated with the development of lower RD with very low certainty of evidence, and the CT genotype was associated with the development of severe RD with very low certainty of evidence.

Regarding the rs3744355 SNP in the *LIG3* gene, one study found association for the development of RD but does not present odds ratio data (89). Another study found that the presence of this SNP decreases the susceptibility of severe RD (92).

The *LIG3* gene encodes components that participate in the DNA repair pathway by base excision (89,104,105). This pathway helps in single-strand repair and double-strand break repair resulting from exposure to reactive oxygen species and free radicals that are produced during exposure to ionizing radiation (89,105). Genetic variants in the *LIG4* gene, which is from the *LIG3* gene family, have already demonstrated a significant association with radiation-induced pneumonitis (106).The SNP in the *LIG3* gene was not included in the prevalence or association meta-analysis, in this systematic review, because there was insufficient data for this.

As there are only two studies that present data of significance for the SNPs rs8193 and rs3744355 and with controversial data, we may not say that these SNPs can be used to predict RD. We also cannot say that the other SNPs that were associated in only one individual study can predict RD.

The proportion meta-analysis showed that the most prevalent SNP in the breast cancer patients that presented RD was rs1800469 in the *TGFβ1* gene, but with a very large confidence interval (41%; 95%CI: 23-60).

The first candidate gene analysis to verify the potential of SNPs to predict radiotoxicity was performed by evaluating genes that act in the inflammatory pathway

(107). SNP rs1800469 is located in the promoter region of the *TGFβ1* gene. The *TGFB1* gene encodes an inflammatory and pro-fibrotic cytokine that repairs DNA damage, in the early stages of wound healing, and in the repair process of injuries induced by ionizing radiation and fibrosis (108). It has not yet been confirmed whether the SNP rs1800469 in the *TGFβ1* gene affects the expression of this protein (109).

Two meta-analysis were performed to assess the potential of SNP rs1800469 to predict the development of late RD in breast cancer patients (109) and the development of any late radiotherapy-induced toxicity (110) but did not confirm this hypothesis. Other studies have found association between the rs1800469 SNP in the *TGFβ1* gene and the development of radiotherapy-induced esophagitis in lung cancer patients (111), and the T allele in this SNP was associated with the occurrence of radiation-induced pneumonitis in patients with thoracic tumors (112).

The SNP rs3957356 in the *GSTA1* gene was the second most prevalent polymorphism in this review (36%). Exposure to ionizing radiation promotes an increase in free radicals that cause tissue damage. The *GSTA* gene is involved in reactive oxygen species pathways, along with other genes in the *GST* family, and encodes antioxidants that scavenge free radicals (113). Therefore, it is hypothesized that alterations in the function of this gene may promote greater radiosensitivity (113). One cohort study found no significant association between the rs3957356 SNP in the *GSTPA1* gene and the occurrence of radiotherapy-induced osteoradionecrosis (114). In this review, the meta-analysis of the association of CT genotype of SNP rs3957356 in *GSTA1* gene with RD severity showed that carriers of this genotype are approximately 6 times more likely to develop severe RD with low certainty of evidence.

MAT1A gene synthesizes a molecule that acts on DNA methylation pathways. (115). Changes in *MAT1A* expression can cause oxidative stress (88). In this review, we found that the GG genotype of SNP rs2282367 in the *MAT1A* gene influenced the severe RD with low certainty of evidence. However, the prevalence assessment of this SNP showed it was present in 27% of breast cancer patients who presented RD.

Six studies included in this review found a statistically significant association between SNP haplotypes investigated in each of them and the development of RD (80, 82, 87, 92-94). Haplotype analyzes show the potential for interactions between allelic variants to modify phenotypes (61,113). However, the haplotypes analyzed in the

studies included in this review are very heterogeneous, which makes it difficult to recommend their use as RD predictors in patients with breast cancer.

It is important to consider the prevalence of SNPs in different geographic regions and ethnicities, given that this frequency of alleles may be different (53,60,61). Although we have studies included in the prevalence meta-analysis that were carried out in different countries, most SNPs were evaluated in only one study for each country, which limited the assessment of prevalence in different geographic regions.

The prevalence of SNPs in breast cancer patients who presented RD ranged from 24 to 41%. All studies showed high inconsistency and heterogeneity. However, the heterogeneity was expected considering that the meta-analyses were performed with few studies, from different locations, and with different sample sizes. Another limitation of this systematic review is that most SNPs were evaluated in only one study and needed to be excluded from meta-analyses. Most of the meta-analyses of association of SNPs with severe RD that were significant included only 2 studies. The association of the CT genotype of SNP rs3957356 in the *GSTA1* gene and the GG genotype of the rs2282367 polymorphism in the *MAT1A* gene had low certainty of evidence. All other SNP genotypes associated with severe or lower RD had very low certainty of evidence.

5.6. CONCLUSION

Significant data show that genotyping of SNPs may be a strategy for predicting radiation dermatitis in breast cancer patients. It is suggested that studies of high methodological rigor to evaluate SNPs that presented high prevalend and that demonstrated a first possibility of association with radiation dermatitis be performed to confirm this hypothesis. Furthermore, studies with populations of different ethnicities and geographic locations are needed to assess SNPs in various populations.

5.7. OTHER INFORMATION

5.7.1. Registration and Protocol

The protocol of this review was submitted for registration in the *International Prospective Registry of Systematic Reviews* (PROSPERO).

5.7.2. Support

The first author (BRLA) is supported by a scholarship in the Graduate Program in Health Sciences at the University of Brasília, by the Coordenação de Aperfeiçoamento de Nível Superior (CAPES), Brazil. CAPES had no role in the study design and interpretation of results. This research did not receive funding from agencies.

5.7.3. Competing Interests

The authors declare that there are no conflicts of interest.

5.7.4. Availability of data, code, and other materials

Appendices can be accessed in the supplementary material of the article.

5.8. APPENDIX

5.8.1. Appendix 1 - Search strategy performed in databases CINAHL, COCHRANE CENTRAL, EMBASE, GOOGLE SCHOLAR, LILACS, OPEN GREY, PUBMED, PROQUEST Thesis & Dissertations, SCOPUS and WEB OF SCIENCE on May 31st, 2021.

Database	Search Strategy	Results
CINAHL	TX ("breast neoplasms" OR "breast" OR "breast tumor" OR "breast tumors" OR "breast tumour" OR "breast tumours" OR "breast cancer" OR "breast cancers" OR "breast carcinoma" OR "breast carcinomas" OR "mammary cancer" OR "mammary cancers" OR "mammary carcinoma" OR "mammary carcinomas") AND TX ("biomarkers" OR "biological markers" OR "biological marker" OR "biomarker" OR "markers" OR "marker" OR "gene" OR "genes" OR "genetic risk score" OR "genetic risk factors" OR "genomic determinants" OR "genetic determinants" OR "genetic predictors" OR "polymorphism, single nucleotide" OR "single nucleotide polymorphism" OR "polymorphism" OR "polymorphisms" OR "polymorphism, genetic" OR "genetic polymorphism" OR "single-nucleotide polymorphisms" OR "polymorphic variants" OR "polymorphic variations" OR "genetic variants" OR "genetic variation" OR "genetic susceptibility" OR "genetic marker" OR "gene expression" OR "SNP" OR "radiogenomics") AND TX ("radiodermatitis" OR	963

	"radiation dermatitis" OR "radioepidermitis" OR "radiation reaction" OR "radio-epithelitis" OR "acute radiation reactions" OR "radiation-induced acute skin" OR "radio-induced damage" OR "cutaneous radiation syndrome" OR "radiodermatitides" OR "radiation-induced dermatitis" OR "radiation-induced skin lesions" OR "radiation induced acute toxicity" OR "radiation-induced toxicity" OR "radiation-induced toxicities" OR "radiation-induced normal tissue toxicity" OR "skin reaction" OR "skin reactions" OR "skin toxicity" OR "skin toxicities" OR "radiation-induced side effects" OR "radiation toxicity" OR "tissue complications" OR "radiation injury" OR "erythema" OR "moist desquamation" OR "dry desquamation")	
COCHRANE CENTRAL	75 Trials matching "breast neoplasms" OR "breast" OR "breast tumor" OR "breast tumors" OR "breast tumour" OR "breast tumours" OR "breast cancer" OR "breast cancers" OR "breast carcinoma" OR "breast carcinomas" OR "mammary cancer" OR "mammary cancers" OR "mammary carcinoma" OR "mammary carcinomas" in All Text AND "biomarkers" OR "biological markers" OR "biological marker" OR "biomarker" OR "markers" OR "marker" OR "gene" OR "genes" OR "genetic risk score" OR "genetic risk factors" OR "genomic determinants" OR "genetic determinants" OR "genetic predictors" OR "polymorphism, single nucleotide" OR "single nucleotide polymorphism" OR "polymorphism" OR "polymorphisms" OR "polymorphism, genetic" OR "genetic polymorphism" OR "single-nucleotide polymorphisms" OR "polymorphic variants" OR "polymorphic variations" OR "genetic variants" OR "genetic variation" OR "genetic susceptibility" OR "genetic marker" OR "gene expression" OR "SNP" OR "radiogenomics"	75

	in All Text AND "radiodermatitis" OR "radiation dermatitis" OR "radioepidermitis" OR "radiation reaction" OR "radio-epithelitis" OR "acute radiation reactions" OR "radiation-induced acute skin" OR "radio-induced damage" OR "cutaneous radiation syndrome" OR "radiodermatitides" OR "radiation-induced dermatitis" OR "radiation-induced skin lesions" OR "radiation induced acute toxicity" OR "radiation-induced toxicity" OR "radiation-induced toxicities" OR "radiation-induced normal tissue toxicity" OR "skin reaction" OR "skin reactions" OR "skin toxicity" OR "skin toxicities" OR "radiation-induced side effects" OR "radiation toxicity" OR "tissue complications" OR "radiation injury" OR "erythema" OR "moist desquamation" OR "dry desquamation" in All Text - (Word variations have been searched)	
EMBASE	('breast neoplasms'/de OR 'breast neoplasms' OR 'breast'/de OR 'breast' OR 'breast cancer'/de OR 'breast cancer' OR 'breast carcinoma'/de OR 'breast carcinoma' OR 'mammary cancer'/de OR 'mammary cancer' OR 'mammary carcinoma'/de OR 'mammary carcinoma') AND ('biomarkers'/de OR 'biomarkers' OR 'biomarker'/de OR 'biomarker' OR 'markers' OR 'marker'/de OR 'marker' OR 'genetic predictors' OR 'single nucleotide polymorphism'/de OR 'single nucleotide polymorphism' OR 'polymorphism'/de OR 'polymorphism' OR 'polymorphisms' OR 'polymorphic variants' OR 'polymorphic variations' OR 'genetic variants' OR 'genetic variation'/de OR 'genetic variation' OR 'snp'/de OR 'snp') AND ('radiodermatitis'/de OR 'radiodermatitis' OR 'radiation dermatitis'/de OR 'radiation dermatitis' OR 'radiation-	448

	induced dermatitis' OR 'radiation-induced skin lesions' OR 'radiation induced acute toxicity' OR 'radiation-induced toxicity' OR 'radiation-induced toxicities' OR 'skin reaction'/de OR 'skin reaction' OR 'skin toxicity'/de OR 'skin toxicity' OR 'radiation toxicity'/de OR 'radiation toxicity')	
GOOGLE SCHOLAR	(“Breast Cancer”) AND (“Biomarkers” OR “Polymorphism, Single Nucleotide” OR “Polymorphism”) AND (“Radiodermatitis")	240
LILACS	(“Carcinoma de Mama in situ” OR “Breast Carcinoma In Situ” OR “Carcinoma Ductal de Mama” OR “Carcinoma, Ductal, Breast” OR “Neoplasias da Mama” OR “Breast Neoplasms” OR “Neoplasias de la Mama”) AND (“Marcadores Genéticos” OR “Genetic Markers” OR “Biomarcadores” OR “Biomarkers” OR “Polimorfismo de Nucleotídeo Único” OR “Polymorphism, Single Nucleotide” OR “Polimorfismo de Nucleótido Simple” OR “Polimorfismo Genético” OR “Polymorphism, Genetic”) AND (“Radiodermatite” OR “Radiodermatitis")	0
OPEN GREY	(“Breast Cancer”) AND (“Biomarkers” OR “Polymorphism, Single Nucleotide” OR “Polymorphism”) AND (“Radiodermatitis")	0
PUBMED	("breast neoplasms"[MeSH Terms] OR "breast neoplasms"[All Fields] OR "breast"[MeSH Terms] OR "breast"[All Fields] OR "breast tumor"[All Fields] OR "breast tumors"[All Fields] OR "breast tumour"[All Fields] OR "breast tumours"[All Fields] OR "breast cancer"[All Fields] OR "breast cancers"[All Fields] OR "breast carcinoma"[All Fields] OR "breast	223

carcinomas"[All Fields] OR "mammary cancer"[All Fields] OR "mammary cancers"[All Fields] OR "mammary carcinoma"[All Fields] OR "mammary carcinomas"[All Fields]) AND ("biomarkers"[MeSH Terms] OR "biomarkers"[All Fields] OR "biological markers"[All Fields] OR "biological marker"[All Fields] OR "biomarker"[All Fields] OR "markers"[All Fields] OR "marker"[All Fields] OR "gene"[All Fields] OR "genes"[All Fields] OR "genetic risk score"[All Fields] OR "genetic risk factors"[All Fields] OR "genomic determinants"[All Fields] OR "genetic determinants"[All Fields] OR "genetic predictors"[All Fields] OR "polymorphism, single nucleotide"[MeSH Terms] OR "polymorphism single nucleotide"[All Fields] OR "single nucleotide polymorphism"[All Fields] OR "polymorphism"[All Fields] OR "polymorphisms"[All Fields] OR "polymorphism, genetic"[MeSH Terms] OR "polymorphism genetic"[All Fields] OR "genetic polymorphism"[All Fields] OR "single-nucleotide polymorphisms"[All Fields] OR "polymorphic variants"[All Fields] OR "polymorphic variations"[All Fields] OR "genetic variants"[All Fields] OR "genetic variation"[All Fields] OR "genetic susceptibility"[All Fields] OR "genetic marker"[All Fields] OR "gene expression"[All Fields] OR "SNP"[All Fields] OR "radiogenomics"[All Fields]) AND ("radiodermatitis"[MeSH Terms] OR "radiodermatitis"[All Fields] OR "radiation dermatitis"[All Fields] OR "radioepidermitis"[All Fields] OR "radiation reaction"[All Fields] OR "radio-epithelitis"[All Fields] OR "acute radiation reactions"[All Fields] OR "radiation-induced acute skin"[All Fields] OR "radio-induced damage"[All Fields] OR "cutaneous radiation syndrome"[All Fields] OR "radiodermatitides"[All Fields] OR "radiation-induced dermatitis"[All Fields] OR "radiation-induced skin lesions"[All Fields] OR "radiation induced

	acute toxicity"[All Fields] OR "radiation-induced toxicity"[All Fields] OR "radiation-induced toxicities"[All Fields] OR "radiation-induced normal tissue toxicity"[All Fields] OR "skin reaction"[All Fields] OR "skin reactions"[All Fields] OR "skin toxicity"[All Fields] OR "skin toxicities"[All Fields] OR "radiation-induced side effects"[All Fields] OR "radiation toxicity"[All Fields] OR "tissue complications"[All Fields] OR "radiation injury"[All Fields] OR "erythema"[All Fields] OR "moist desquamation"[All Fields] OR "dry desquamation"[All Fields])	
PROQUEST Thesis & Dissertations	("breast neoplasms" OR "breast" OR "breast tumor" OR "breast tumour" OR "breast cancer" OR "breast cancers" OR "breast carcinoma" OR "mammary cancer" OR "mammary carcinoma") AND ("biomarkers" OR "biomarker" OR "markers" OR "marker" OR "gene" OR "genes" OR "genomic determinants" OR "genetic determinants" OR "single nucleotide polymorphism" OR "polymorphism" OR "polymorphisms" OR "single-nucleotide polymorphism" OR "polymorphic variants" OR "polymorphic variations" OR "genetic variants" OR "genetic variation" OR "genetic susceptibility" OR "genetic marker" OR "gene expression" OR "SNP") AND ("radiodermatitis" OR "radiation dermatitis" OR "radiation-induced skin reactions")	105
SCOPUS	TITLE-ABS-KEY (("breast neoplasms" OR "breast" OR "breast tumor" OR "breast tumors" OR "breast tumour" OR "breast tumours" OR "breast cancer" OR "breast cancers" OR "breast carcinoma" OR "breast carcinomas" OR "mammary cancer" OR "mammary cancers" OR "mammary carcinoma" OR "mammary	703

	carcinomas") AND ("biomarkers" OR "biological markers" OR "biological marker" OR "biomarker" OR "markers" OR "marker" OR "gene" OR "genes" OR "genetic risk score" OR "genetic risk factors" OR "genomic determinants" OR "genetic determinants" OR "genetic predictors" OR "polymorphism, single nucleotide" OR "single nucleotide polymorphism" OR "polymorphism" OR "polymorphisms" OR "polymorphism, genetic" OR "genetic polymorphism" OR "single-nucleotide polymorphisms" OR "polymorphic variants" OR "polymorphic variations" OR "genetic variants" OR "genetic variation" OR "genetic susceptibility" OR "genetic marker" OR "gene expression" OR "snp" OR "radiogenomics") AND ("radiodermatitis" OR "radiation dermatitis" OR "radioepidermitis" OR "radiation reaction" OR "radio-epithelitis" OR "acute radiation reactions" OR "radiation-induced acute skin" OR "radio-induced damage" OR "cutaneous radiation syndrome" OR "radiodermatitides" OR "radiation-induced dermatitis" OR "radiation-induced skin lesions" OR "radiation induced acute toxicity" OR "radiation-induced toxicity" OR "radiation-induced toxicities" OR "radiation-induced normal tissue toxicity" OR "skin reaction" OR "skin reactions" OR "skin toxicity" OR "skin toxicities" OR "radiation-induced side effects" OR "radiation toxicity" OR "tissue complications" OR "radiation injury" OR "erythema" OR "moist desquamation" OR "dry desquamation")) AND (LIMIT-TO (DOCTYPE , "ar"))	
WEB OF SCIENCE	TÓPICO: (("breast neoplasms" OR "breast" OR "breast tumor" OR "breast tumors" OR "breast tumour" OR "breast tumours" OR "breast cancer" OR "breast cancers" OR "breast carcinoma" OR "breast carcinomas" OR "mammary cancer" OR "mammary cancers" OR	269

"mammary carcinoma" OR "mammary carcinomas") AND ("biomarkers" OR "biological markers" OR "biological marker" OR "biomarker" OR "markers" OR "marker" OR "gene" OR "genes" OR "genetic risk score" OR "genetic risk factors" OR "genomic determinants" OR "genetic determinants" OR "genetic predictors" OR "polymorphism, single nucleotide" OR "single nucleotide polymorphism" OR "polymorphism" OR "polymorphisms" OR "polymorphism, genetic" OR "genetic polymorphism" OR "single-nucleotide polymorphisms" OR "polymorphic variants" OR "polymorphic variations" OR "genetic variants" OR "genetic variation" OR "genetic susceptibility" OR "genetic marker" OR "gene expression" OR "SNP" OR "radiogenomics") AND ("radiodermatitis" OR "radiation dermatitis" OR "radioepidermitis" OR "radiation reaction" OR "radio-epithelitis" OR "acute radiation reactions" OR "radiation-induced acute skin" OR "radio-induced damage" OR "cutaneous radiation syndrome" OR "radiodermatitides" OR "radiation-induced dermatitis" OR "radiation-induced skin lesions" OR "radiation induced acute toxicity" OR "radiation-induced toxicity" OR "radiation-induced toxicities" OR "radiation-induced normal tissue toxicity" OR "skin reaction" OR "skin reactions" OR "skin toxicity" OR "skin toxicities" OR "radiation-induced side effects" OR "radiation toxicity" OR "tissue complications" OR "radiation injury" OR "erythema" OR "moist desquamation" OR "dry desquamation"))

Índices=SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, ESCI Tempo estipulado=Todos os anos

5.8.2. Appendix 2 – Excluded articles and reason for exclusion

5.8.2.1. Appendix 2.1 – Excluded articles in databases searching (n=48)

Authors	Reason for exclusion
1. Alexopoulou et al, 2018	4
2. Andreassen et al, 2014	8
3. Azimian et al, 2018	8
4. Badie et al, 2008	8
5. Baijer et al, 2016	8
6. Barber et al, 2000	8
7. Batar et al, 2016	8
8. Bremer et al, 2003	3
9. Clarke et al, 1998	8
10. Córdoba et al, 2018	8
11. Drobin et al, 2020	9
12. Falvo et al, 2011	4
13. Fogarty et al, 2010	9
14. Green et al, 2002	4
15. Guerci et al, 2014	8
16. Haffty et al, 2012	8
17. Haghdoost t al, 2001	3
18. Hu et al, 2018	3
19. Hu et al, 2015	8

20. Huszno et al, 2013	3
21. Huszno et al, 2015	3
22. Iannuzzi et al, 2002	3
23. Isomura et al, 2008	8
24. Jones et al, 1995	8
25. Jung et al, 2015	3
26. Katsila et al, 2017	8
27. Leong et al, 2000	3
28. Lincz et al, 2009	3
29. Mangoni et al, 2009	8
30. Moullan et al, 2003	7
31. Mullins et al, 2019	8
32. Oliva, Nilsson, et al, 2018	6
33. Oliva et al, 2018	8
34. Oppitz et al, 1999	9
35. Palumbo et al, 2019	2
36. Park et al, 2014	3
37. Popanda et al, 2009	8
38. Rattay et al, 2016	8
39. Rattay et al, 2020	8
40. Reuther et al, 2015	8
41. Rodriguez- Gil et al, 2011	8
42. Rodriguez-Gil et al, 2014	3
43. Rosenstein et al, 2011	8

44. Sanctis et al, 2014	3
45. Skiöld et al, 2013	8
46. Sterpone et al, 2010	8
47. Talbot et al, 2012	4
48. Thomas et al, 2011	8

Reason for exclusion:

(1) Studies in patients with other types of primary cancer undergoing radiation therapy, that are not breast cancer (n = 0);

(2) Studies that include patients with different types of cancer undergoing radiotherapy do not show individual results for breast cancer patients (n = 1);

(3) No single nucleotide polymorphism reported (n = 12);

(4) Studies than report analysis for radiation dermatitis evaluated after 3 months of the end of radiotherapy / chronic radiation dermatitis (n = 4);

(5) No association between single nucleotide polymorphism and risk of development of acute radiation dermatitis or severity of acute radiation dermatitis (n = 0);

(6) Studies that reported only association between single nucleotide polymorphism and symptoms of acute radiation dermatitis, and not the signs (n = 1);

(7) Data not individualized for acute radiation dermatitis (n = 1);

(8) Experimental studies (In vitro, in vivo animal studies or clinical trials), descriptive studies, cross-sectional studies, case-control studies, reviews, letters, chapters, personal opinions, conference abstracts, thesis and dissertations (n = 26);

(9) Studies that did not report sufficient information (n = 3).

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5.8.2.2. Appendix 2.2 – Excluded articles in gray literature Searching (n=6)

Authors	Reason for exclusion
1. Castiblanco et al, 2016	2
2. Córdoba, 2017	8
3. Derda, 2011	8
4. Greve, 2009	8
5. Huang et al, 2008	8
6. Wang, 2011	8

Reason for exclusion:

(1) Studies in patients with other types of primary cancer undergoing radiation therapy, that are not breast cancer (n = 0);

(2) Studies that include patients with different types of cancer undergoing radiotherapy do not show individual results for breast cancer patients (n = 1);

(3) No single nucleotide polymorphism reported (n = 0);

(4) Studies than report analysis for radiation dermatitis evaluated after 3 months of the end of radiotherapy / chronic radiation dermatitis (n = 0);

(5) No association between single nucleotide polymorphism and occurrence of acute radiation dermatitis or severity of acute radiation dermatitis (n = 0);

(6) Studies that reported only association between single nucleotide polymorphism and symptoms of acute radiation dermatitis, and not the signals (n = 0);

(7) Data not individualized for acute radiation dermatitis (n = 0);

(8) Experimental studies (In vitro, in vivo animal studies or clinical trials), descriptive studies, cross-sectional studies, case-control studies, reviews, letters, chapters, personal opinions, conference abstracts, thesis and dissertations (n = 5);

(9) Studies that did not report sufficient information (n = 0).

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5.8.3. Appendix 3 – Judgement of risk of bias in individual studies according to Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cohort Studies (77)

Study: Ahn et al, 2006 (80)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Yes	Low	The groups were recruited from the same population and the study report that the characteristics of the study population were similar.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Blood samples from all patients were collected before RT.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	The study used the Sequenom's (San Diego, CA) high-throughput matrix-assisted laser desorption/ ionization time-of-flight mass spectrometry to assess polymorphisms.
Q4 - Were confounding factors identified?	Yes	Low	The differences in treatment by various hospitals, for BMI, smoking status, alcohol consumption, and hormonal therapies received were considered potential confounding factors.
Q5 - Were strategies to deal with confounding factors stated?	Yes	Low	Women were excluded if they were currently or ever treated with CT. The differences in treatment by various hospitals were adjusted in the minimally adjusted model. Adjusted models were further adjusted for BMI, smoking status, alcohol consumption, and hormonal therapies received.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Low	Caucasian female breast cancer patients receiving primary RT after conserving surgery were recruited. The patients did not present RD at the recruitment moment.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	The study used The Common Toxicity Criteria version 2.0 modified to evaluate the grade of the RD for all patients.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	The skin of all patients were evaluated at the end RT.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	The study included 478 patients. However, blood samples collected before starting RT were available for 446 patients.
Q10 - Were strategies to address incomplete follow up utilized?	Yes	Low	Only patients whose blood samples collected before starting RT were available were included in this analysis.
Q11- Was appropriate statistical analysis used?	Yes	Low	The effects were evaluated using Cox proportional hazards models. Multivariate models were used for some variants.

BMI: Body Mass Index; RT: Radiotherapy; CT: Chemotherapy; RD: Radiation Dermatitis.

Study: Ambrosone et al, 2006 (81)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Yes	Low	The groups were recruited from the same population and the study report that the characteristics of the study population were similar.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Blood samples from all patients were collected before RT.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	The study used the Sequenom's (San Diego, CA) high-throughput matrix-assisted laser desorption/ ionization time-of-flight mass spectrometry PCR and multiplex PCR technique to assess polymorphisms.
Q4 - Were confounding factors identified?	Yes	Low	The treatment algorithm was slightly different across four clinics, and photon-field and boost methods are considered the additional factors affecting toxicity. Therefore, they were considered as confounding factors in addition to clinical characteristics.
Q5 - Were strategies to deal with confounding factors stated?	Yes	Low	Women who were currently or ever treated with CT were excluded. The Cox regression analysis was conducted adjusted for photon and boost methods, as well as stratified by clinic.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Low	Caucasian female breast cancer patients receiving primary RT of the breast after breast conserving surgery were recruited. The patients did not present RD at the recruitment moment.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	The study used The Common Toxicity Criteria version 2.0 modified to evaluate the grade of the RD for all patients.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	The skin of all patients were evaluated at the end RT.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	The study included 478 patients. However, blood samples collected before starting RT were available for 446 patients.
Q10 - Were strategies to address incomplete follow up utilized?	Yes	Low	Only patients whose blood samples collected before starting RT were available were included in this analysis.
Q11- Was appropriate statistical analysis used?	Yes	Low	The associations analysis were performed using the Cox model and univariate analysis for each factor. Multivariate models were used for those variables that had to be potentially significant ($P < 0.30$) in the univariate analysis.

Legend: RT: Radiotherapy; PCR: Polymerase Chain Reaction; CT: Chemotherapy; RD: Radiation Dermatitis.

Study: Borghini et al, 2014 (82)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	No	High	The groups were recruited from the same population and the characteristics of the study population were similar, except for a significant difference (p = 0.02) that was found in BMI between the groups that developed severe acute RD and those that did not.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Blood samples from all patients were collected before RT.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	*XRCC1* (rs25487) and *XRCC3* (rs861539) polymorphisms were assessed by PCR-RFLP. *GSTM1* and *GSTT1* was carried out in a multiplex PCR.
Q4 - Were confounding factors identified?	Unclear	Moderate	BMI was considered a confounding factor. However, some patients received concomitant CRT and the type of CT did not report. We know that some CTs can influence skin reactions. But the authors did not report this information.
Q5 - Were strategies to deal with confounding factors stated?	Unclear	Moderate	BMI were included in the association analysis between severe acute RD and the polymorphisms. The article did not report the type of CT used by patients neither if the use of CT also was identified and dealed with a confounding factor.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Low	The patients did not present RD at the recruitment moment.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	The authors used a scoring system according to the Radiation Therapy Oncology Group criteria to evaluate skin reaction.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	The occurrence and severity of RD were determined within 30 days after RT treatment.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	All patients were successfully genotyped for polymorphisms.
Q10 - Were strategies to address incomplete follow up utilized?	Not Applicable	Low	All patients were included in the analysis and there were no losses to follow-up.
Q11- Was appropriate statistical analysis used?	Yes	Low	Cox proportional hazard models (hazard ratios with confidence intervals 95%) were used to assess association between severe acute RD and the polymorphisms adjusted for confounding factors.

Legend: BMI: Body Mass Index; RD: Radiation Dermatitis; PCR/RFLP: Polymerase Chain Reaction/Restriction Fragment Length Polymorphism; CRT: Chemoradiotherapy; RT: Radiotherapy; CT: Chemotherapy; *XRCC1:* X-ray repair cross-complementing protein 1; *XRCC3:* X-Ray Repair Cross Complementing 3; *GSTM1:* Glutathione S-Transferase M1; *GSTT1*: Glutathione S-Transferase Theta 1.

Study: Chang-Claude et al, 2005 (83)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Yes	Low	The groups were recruited from the same population and the study report that the characteristics of the study population were similar.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Blood samples from all patients were collected before RT.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	Detection of polymorphisms was done by rapid capillary PCR with melting curve analysis using fluorescence-labeled hybridization probes in a Light- Cycler (Roche Diagnostics, Mannheim, Germany).
Q4 - Were confounding factors identified?	Yes	Low	The treatment algorithm was slightly different across four clinics, and photon-field and boost methods are considered the additional factors affecting toxicity. Therefore, they were considered as confounding factors in addition to clinical characteristics.
Q5 - Were strategies to deal with confounding factors stated?	Yes	Low	Women who were currently or ever treated with CT were excluded. The authors adjusted for differences in radiation dose when severe RD was recorded. The variables, hospital, photon beam energy for whole breast irradiation, and boost irradiation were included in the analysis model. BMI was included as a possible confounder in all models.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Low	Caucasian female breast cancer patients receiving primary RT of the breast after breast conserving surgery were recruited. The patients did not present RD at the recruitment moment.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	The study used The Common Toxicity Criteria version 2.0 modified to evaluate the grade of the RD for all patients.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	The skin of all patients were evaluated at the end RT.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	Because of an inadequate amount of DNA, a few samples did not generate complete information for all polymorphisms.
Q10 - Were strategies to address incomplete follow up utilized?	Yes	Low	Only patients whose blood samples collected before starting RT were available were included in this analysis.
Q11- Was appropriate statistical analysis used?	Yes	Low	The effect of the genetic variants on risk of developing RD was evaluated by Cox proportional hazards model and confounding factors were included in the analysis model.

Legend: RT: Radiotherapy; PCR: Polymerase Chain Reaction; CT: Chemotherapy; RD: Radiation Dermatitis; BMI: Body Mass Index; DNA: Deoxyribonucleic Acid.

Study:Córdoba et al, 2016 (84)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Yes	Low	The groups were recruited from the same population and the characteristics of the study population were similar.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Blood samples and swabbing oral mucosa were collected before RT.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	PCR-RFLP technique was used to evaluate polymorphisms.
Q4 - Were confounding factors identified?	Yes	Low	Neo-adjuvant CT, age, vitamin, and dietary supplements consumed by patients, smoking habits, alcohol consumption, anemia, hypertension, diabetes, and BMI were identified as confounding factors.
Q5 - Were strategies to deal with confounding factors stated?	Unclear	Moderate	The authors found a statistically significant difference between age, BMI, and breast size between patients who had severe or lower acute RD. However, they did not report whether these variables were tested for the association between RD and polymorphisms.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Low	The patients did not present RD in the moment of recruitment.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	The RD was assessed using the Radiation Therapy Oncology Group criteria.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	The severity of RD was determined during and after RT, given the highest degree of toxicity.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	All patients were successfully genotyped for polymorphisms.
Q10 - Were strategies to address incomplete follow up utilized?	Not Applicable	Low	All patients were included in the analysis and there were no losses to follow-up.
Q11- Was appropriate statistical analysis used?	Yes	Low	Odds ratios and their 95%CI were used as estimates of association. Univariate logistic regression analysis evaluated the effect of clinical characteristics and polymorphisms on the severe acute RD.

Legend: RT: Radiotherapy; PCR/RFLP: Polymerase Chain Reaction/Restriction Fragment Length Polymorphism; CT: Chemotherapy; BMI: Body Mass Index; RD: Radiation Dermatitis.

Study: De Langhe et al, 2014 (85)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Yes	Low	The patients were recruited of the two hospitals. The characteristics of the study population were similar between the groups.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Blood samples were collected before start of RT.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	Genotyping was performed using PCR-RFLP analyses, high-resolution melting curve analyses, single base extension techniques or direct sequencing.
Q4 - Were confounding factors identified?	Yes	Low	For the clinical association analysis, univariate analysis was initially carried out to assess the relationship between patients and treatment-related factors and the endpoints.
Q5 - Were strategies to deal with confounding factors stated?	Yes	Low	Patients with and without grade 2 acute RD were compared by means of the Mann–Whitney test for continuous variables and the $\chi 2$-test for categorical variables. Clinical variables with $p < 0.05$ were tested in a multivariate logistic regression analysis.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Low	The patients did not present RD in the moment of recruitment for this study.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	The skin reaction was assessed using the Common Terminology Criteria for Adverse Events version 3.0 scoring system.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	Acute RD was assessed weekly during RT and at 1–2 weeks after RT.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	All patients were successfully genotyped for polymorphisms.
Q10 - Were strategies to address incomplete follow up utilized?	Not Applicable	Low	All patients were included in the analysis and there were no losses to follow-up.
Q11- Was appropriate statistical analysis used?	Yes	Low	To assess the independent effect of each polymorphism, unconditional logistic regression analyses were performed to calculate Odds Ratio. Clinical variables with $p < 0.05$ were tested in a multivariate logistic regression analysis.

Legend: RT: Radiotherapy; PCR/RFLP: Polymerase Chain Reaction/Restriction Fragment Length Polymorphism; RD: Radiation Dermatitis.

Study:Lee et al, 2020 (86)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Yes	Low	The groups were recruited from the same population and the characteristics of the study population were similar.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Blood samples were collected before the first session of RT and after the last session of RT for all patients. Genomic DNA was extracted from frozen whole blood.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	The DNA was screened using the Illumina Human Omni2.5-8 v1 genome-wide BeadChip array (Illumina, San Diego, CA).
Q4 - Were confounding factors identified?	Yes	Low	Variables significantly associated with severe acute RD were considered potential confounding effects.
Q5 - Were strategies to deal with confounding factors stated?	Yes	Low	Variables significantly associated with acute RD were included in the multivariable logistic regression model and in the subsequent association analyses between to control potential confounding effects.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Low	The patients did not present RD in the moment of recruitment for this study.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	The skin reaction was assessed using the standardized Oncology Nursing Society scale.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	The study considered the grade of acute RD assessed at the end of RT as the primary timepoint for outcome measurement.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	All patients were successfully genotyped for polymorphisms.
Q10 - Were strategies to address incomplete follow up utilized?	Not Applicable	Low	All patients were included in the analysis and there were no losses to follow-up.
Q11- Was appropriate statistical analysis used?	Yes	Low	Multivariable analysis revealed that only BMI, surgery, and RT fractionation were independent risk factors for RT-induced RD and these variables were included in subsequent analyses as covariates to control for potential confounding effects. Odds Ratio and 95%CI were reported to determine which polymorphisms drove the significance of the association with severe acute RD.

Legend: RT: Radiotherapy; DNA: Deoxyribonucleic Acid; RD: Radiation Dermatitis; BMI: Body Mass Index.

Study: Mangoni et al, 2011 (87)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Unclear	Moderate	All patients were recruited from the same institution. The clinical characteristics of the patients did not present in the study.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Blood samples were collected before starting RT for all patients.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	Polymorphisms were analyzed by multiplex single nucleotide primer extension using the ABI PRISM SNaPshot Multiplex system (Applied Biosystems, Life Technologies Corporation, USA). The process starts with the amplification of DNA to generate template by PCR.
Q4 - Were confounding factors identified?	Unclear	Moderate	The clinical and individual characteristics of the patients were not described. Although the authors identified the variation in RT parameters as possible confounding factors. Breast size and BMI were not described and increasing the severity of RD as confounding factors.
Q5 - Were strategies to deal with confounding factors stated?	Unclear	Moderate	Analyzes were performed considering the mean BED of RT dose. However, others clinical factors, such as BMI and breast size, were not identified as confounding factors to include in the multivariate analysis.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Low	The patients did not present RD in the moment of recruitment for this study.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	The study used The Common Toxicity Criteria version 2.0 modified to evaluate the grade of the RD for all patients.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	The skin of all patients were evaluated during treatment with RT.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	Ninety-nine patients were included, but only 96 had available blood samples collected before RT. Among them, 87 continued to receive RT at the institution where the study was conducted.
Q10 - Were strategies to address incomplete follow up utilized?	Unclear	Moderate	The study does not report an intention-to-treat analysis considering patients who started receiving RT at another hospital.
Q11- Was appropriate statistical analysis used?	Unclear	Moderate	Occurrence of acute RD was analyzed using Cox proportional hazards model in relation to BED, adjusting for differences in radiation dose. But did not report if they included others confounding factors.

Legend: RT: Radiotherapy; DNA: Deoxyribonucleic Acid; PCR: Polymerase Chain Reaction; CT: Chemotherapy; BMI: Body Mass Index; RD: Radiation Dermatitis; BED: Biologically Effective Radiotherapy Dose.

Study: Mumbrekar et al, 2017 (88)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Yes	Low	The groups were recruited from the same population and the characteristics of the study population were similar.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Blood samples were collected of all patients.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	The TaqMan SNP genotyping assay (Applied Biosystems, Foster City, CA) and PCR was used to genotype the selected polymosphisms.
Q4 - Were confounding factors identified?	Unclear	Moderate	None of the basal characteristics studied were associated with the risk of acute RD. Individual factors such as breast size and BMI were not reported. These clinical features can be confounding factors.
Q5 - Were strategies to deal with confounding factors stated?	Unclear	Moderate	The association between factors related to patient, tumor and treatment with acute RD was tested using Fisher's exact test and these variants were included in the association analysis between SNPs and acute RD. However, factors such as breast size and BMI were not reported.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Unclear	Moderate	It is not clear whether patients were recruited before or after RT, nor at what time the blood sample for analysis of SNPs was collected. The authors only report that 9 patients were lost because they had no skin assessment data. The authors consider the grade of RD developed at the end of the RT as the outcome.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	The severity of the RD was assessed using the Radiation Therapy Oncology Group criteria.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	The study considered the grade of acute RD assessed at the end of RT.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Unclear	Moderate	One hundred thirty-five patients were recruited, but RD data were available for 126 patients who were included in the analyses. The authors did not report the reason for the loss to follow-up of these 9 patients.
Q10 - Were strategies to address incomplete follow up utilized?	Unclear	Moderate	Intention-to-treat analysis was not performed to include available data from the 9 patients who were lost to follow-up. These patients were excluded from the association analysis.
Q11- Was appropriate statistical analysis used?	Yes	Low	To determine the association between SNPs and severe acute RD the odds ratios with 95%CI were calculated using Fisher exact test.

Legend: PCR: Polymerase Chain Reaction; RD: Radiation Dermatitis; BMI: Body Mass Index; SNPs: Single Nucleotide Polymorphisms; RT: Radiotherapy.

Study: Murray et al, 2011 (89)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Unclear	Moderate	The groups were recruited from the same population. However, the study did not report the characteristics of the sample.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Patients provided either a blood or a sputum sample for genotypic analysis, but both samples provide DNA for polymorphism analysis.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	Two SNPs were assessed by Allele Specific Oligonucleotide (ASO) hybridization and three SNPs were analysed by SNPlex™ Genotyping.
Q4 - Were confounding factors identified?	Unclear	Moderate	The article presents linear regression analysis considering RT dose or breast size as a confounding factor. However, the patients who make up the sample were recruited from 3 centers and data such as BMI and use of concomitant CT were not presented.
Q5 - Were strategies to deal with confounding factors stated?	Unclear	Moderate	It is not possible to verify whether BMI and use of concomitant CT could influence the development of severe acute RD.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Low	This is a retrospective cohort. It is unclear whether the blood or sputum sample was collected before or after the patients had RD.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	The study used The Common Toxicity Criteria version 3.0 modified to evaluate the grade of the RD for all patients.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	The skin of all patients was evaluated at the end RT.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	The follow up did not complete. However, the article reported that 54 samples with rates below 75% across all 43 SNPs typed in the study indicating the DNA quality from those might compromise the results.
Q10 - Were strategies to address incomplete follow up utilized?	Unclear	Moderate	The authors reported that 54 samples with call rates below 75% were removed from the genetic analysis. However, they did not present the analysis that make it possible to verify if they used strategies to address incomplete follow up.
Q11- Was appropriate statistical analysis used?	Unclear	Moderate	Association, regression and principal components analysis were performed. The article did not present the association analysis data between polymorphisms and severe acute RD. Therefore, it is not possible to evaluate whether a correct statistical analysis was made.

Legend: DNA: Deoxyribonucleic Acid; SNPs: Single Nucleotide Polymorphisms; RT: Radiotherapy; BMI: Body Mass Index; CT: Chemotherapy; RD: Radiation Dermatitis.

Study: Popanda et al, 2006 (90)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Yes	Low	The groups were recruited from the same population and the study report a reference showing that the characteristics of the sample were similar.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Blood samples from all patients were collected before RT.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	DNA extraction, analysis of the *one* polymorphism was assessed by PCR–RFLP and the *two* polymorphisms were assessed by PCR with melting curve analysis of sequence-specific hybridization probes.
Q4 - Were confounding factors identified?	Yes	Low	Differences by treating hospitals and BMI were considered potential confounding factors.
Q5 - Were strategies to deal with confounding factors stated?	Yes	Low	Women were excluded if they were currently or ever treated with CT to avoid potential confounding. Confounding factors were included in all analysis models.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Low	Caucasian female breast cancer patients receiving primary RT of the breast after breast conserving surgery were recruited. The patients did not present RD at the recruitment moment.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	The study used The Common Toxicity Criteria version 2.0 modified to evaluate the grade of the RD for all patients.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	The skin of all patients was evaluated at the end RT.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	The study included 478 patients. However, blood samples collected before RT were available for 446 patients. Two samples had inadequate amount of DNA that presented incomplete genotype information.
Q10 - Were strategies to address incomplete follow up utilized?	Unclear	Moderate	It is not clear from the study whether only 444 patients who had enough DNA were included in the analysis. The study reports that 77 of the 446 patients included in the study had severe acute RD, but it does not report the degree of RD of the 2 missing patients.
Q11- Was appropriate statistical analysis used?	Yes	Low	Occurrence of acute severe RD was analyzed using Cox proportional hazards model in relation to BED. Confounding factors were included in all models.

Legend: RT: Radiotherapy; DNA: Deoxyribonucleic Acid; PCR/RFLP: Polymerase Chain Reaction/Restriction Fragment Length Polymorphism; PCR: Polymerase Chain Reaction; BMI: Body Mass Index; CT: Chemotherapy; RD: Radiation Dermatitis; BED: Biologically Effective Radiotherapy Dose.

Study: Raabe et al, 2012 (91)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Yes	Low	Patients were recruited from more than one institution. However, the author reported that clinical characteristics were similar for the sample (data not shown).
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Blood samples from all patients were collected.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	Polymorphisms were determined using either the PCR-RFL or MALDI-TOF technique.
Q4 - Were confounding factors identified?	No	High	The study identified that there was no statistically significant difference between the RT characteristics with the severe RD. Breast volume was the only statistically significant variable for RD severity. The authors did not report that these is potential confounding factors.
Q5 - Were strategies to deal with confounding factors stated?	Unclear	Moderate	Analyses were performed using all patients and subgroups stratified by breast volume. Breast volume was the only statistically significant variable for RD severity. No adjustment was performed for multiple testing.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Unclear	Moderate	It is not clear whether patients were recruited before or after RT, nor at what time the blood sample for analysis of SNPs was collected.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	Erythema of the breast was evaluated using the Radiation Therapy Oncology Group score.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	At 50 Gy, prior to boost application, erythema of the breast, excluding folds and scars, was evaluated.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	All patients were successfully genotyped for polymorphisms.
Q10 - Were strategies to address incomplete follow up utilized?	Not Applicable	Low	All patients were included in the analysis.
Q11- Was appropriate statistical analysis used?	Yes	Low	Associations between severe acute RD and each individual SNP were tested using odds ratio and 95%CI using logistic regression. Analyses were performed using all patients and subgroups stratified by breast volume. No adjustment was performed for multiple testing.

Legend: PCR/RFLP: Polymerase Chain Reaction/Restriction Fragment Length Polymorphism; MALDI-TOF: Matrix-Assisted-Laser-Desorption/Ionization–Time-Of-Flight-Mass-Spectrometry; RT: Radiotherapy; RD: Radiation Dermatitis; SNPs: Single Nucleotide Polymorphisms.

Study: Suga et al, 2007 (92)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Yes	Low	The groups were recruited from the same population and the characteristics of the study sample were similar, except for the age distribution. However, mean age and standard deviation were similar.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Blood samples were collected of all patients.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	SNPs typing was performed using the MassARRAY system (Sequenom, San Diego, CA) and PCR.
Q4 - Were confounding factors identified?	Unclear	Moderate	In the present study patients who underwent mastectomy were excluded, and the collaborating institutions were all equipped with appropriate treatment modalities and performed breast-conserving RT with linear-accelerated electron facilities. Other variables such as BMI and breast size did not report as confounding factor.
Q5 - Were strategies to deal with confounding factors stated?	Unclear	Moderate	The patients were not stratified any further for this genetic analysis. The article does not report whether multivariate analysis was performed to deal with confounding factors.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Unclear	Moderate	It is not clear whether patients were recruited before or after RT, nor at what time the blood sample for analysis of SNPs was collected.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	The study used The Common Toxicity Criteria version 2.0 to evaluate RD.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	The skin of all patients was evaluated within 3 months of RT initiation.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	All patients were successfully genotyped for polymorphisms.
Q10 - Were strategies to address incomplete follow up utilized?	Not Applicable	Low	All patients were included in the analysis.
Q11- Was appropriate statistical analysis used?	Yes	Low	The associations between the grade of RD and each of the SNPs or haplotypes were assessed using the two tailed Fisher exact test and odds ratio and confidence interval, respectively.

Legend: PCR: Polymerase Chain Reaction; SNPs: Single Nucleotide Polymorphisms; RT: Radiotherapy; RD: Radiation Dermatitis.

Study: Tan et al, 2006 (93)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Yes	Low	The groups were recruited from the same population. The study reports a reference showing that the sample characteristics were similar.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Blood samples from all patients were collected before RT.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	One polymorphism was identified using a standard PCR protocol. *Two* polymorphisms were determined by rapid capillary PCR with melting curve analysis using fluorescence labeled hybridization probes in a LightCycler (Roche Diagnostics, Germany).
Q4 - Were confounding factors identified?	Yes	Low	The differences in treatment by various hospitals, dose received, and BMI were considered potential confounding factors.
Q5 - Were strategies to deal with confounding factors stated?	Yes	Low	Women were excluded if they were currently or ever treated with CT to avoid potential confounding. The differences in treatment dose by various hospitals were adjusted by including hospital and photon BED for whole breast and for boost irradiation. Adjusted models were used for BMI.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Low	Caucasian female breast cancer patients receiving primary RT of the breast after breast conserving surgery were recruited. The patients did not present RD at the recruitment moment.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	The study used The Common Toxicity Criteria version 2.0 modified to evaluate the grade of the RD for all patients.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	The skin of all patients was evaluated at the end RT.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	Blood samples collected before RT were available for 446 patients included in the analysis. One blood sample did not generate complete genotype information because of an inadequate amount of DNA.
Q10 - Were strategies to address incomplete follow up utilized?	Unclear	Moderate	The study reports that 77 of the 446 patients included in the study had severe acute RD, but it does not report the grade of RD of the 1 missing patients.
Q11- Was appropriate statistical analysis used?	Yes	Low	The effects of the genetic variants on the risk of developing clinical radiotoxicity were evaluated using Cox proportional hazards models. Adjusted models were used for confounding factors.

Legend: RT: Radiotherapy; PCR: Polymerase Chain Reaction; BMI: Body Mass Index; DNA: Deoxyribonucleic Acid; CT: Chemotherapy; BED: Biologically Effective Radiotherapy Dose.

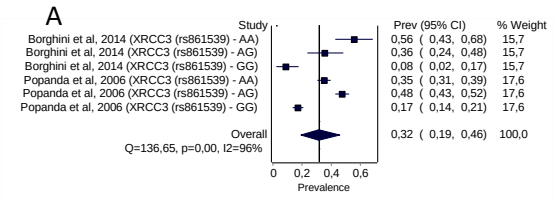
Study: Terrazzino et al, 2012 (94)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Yes	Low	The groups were recruited from the same population and the characteristics of the study sample were similar.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Although this is a retrospective study, for data analysis we used blood samples from all patients collected before RT.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	*Two* polymorphisms, were determined by real-time PCR allelic discrimination assay, and one polymorphism was genotyped according to PCR-RFLP methods.
Q4 - Were confounding factors identified?	Yes	Low	Potential confounding factors evaluated: age, BMI, breast diameter, smoking status, diabetes, hypertension, history of vasculopathy, and alcohol consumption. Dosimetric factors were also analyzed.
Q5 - Were strategies to deal with confounding factors stated?	Yes	Low	The explanatory variables with a cut-off of P-value <0.1 from univariate analyses were used and included into the multivariate logistical regression model to identify independent predictors of acute RD. The classification table was used to evaluate the predictive accuracy of the final logistic regression model.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Low	The patients did not present RD at the recruitment moment.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	Skin reaction was evaluated using the Radiation Therapy Oncology Group score.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	The occurrence and severity of RD were determined during and after the end of RT considering the highest grade of toxicity.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	All patients were successfully genotyped for polymorphisms.
Q10 - Were strategies to address incomplete follow up utilized?	Yes	Low	All patients were included in the analysis.
Q11- Was appropriate statistical analysis used?	Yes	Low	The effect of clinical factors and genetic variables on the risk of severe acute RD was first evaluated by univariate logistic regression analysis. Odds ratios and their 95%CI were used as association estimate.

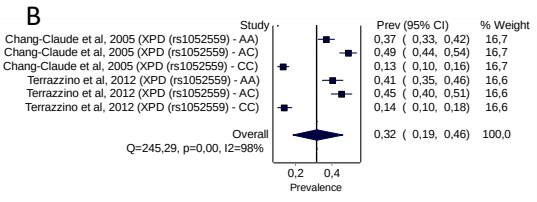
Legend: RT: Radiotherapy; *MSH2 MSH3;* PCR: Polymerase Chain Reaction; PCR/RFLP: Polymerase Chain Reaction/Restriction Fragment Length Polymorphism; BMI: Body Mass Index; RD: Radiation Dermatitis.

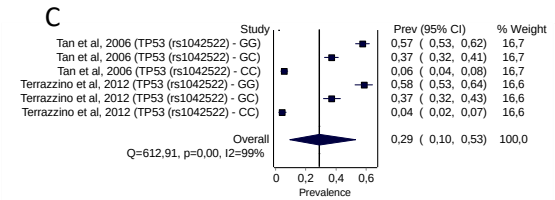
Study: Zhou et al, 2010 (95)			
Question	**Judgment**	**Risk of Bias**	**Comments**
Q1 - Were the two groups similar and recruited from the same population?	Yes	Low	The groups were recruited from the same population and the characteristics of the study sample were similar.
Q2 - Were the exposures measured similarly to assign people to both exposed and unexposed groups?	Yes	Low	Blood samples from all patients were collected before RT.
Q3 - Was the exposure measured in a valid and reliable way?	Yes	Low	Genotypes were analyzed by PCR-RFLP.
Q4 - Were confounding factors identified?	Unclear	Moderate	The article did not report if BMI and breast size were considered as confounding factors.
Q5 - Were strategies to deal with confounding factors stated?	Unclear	Moderate	The association between polymorphisms and severe acute RD analysis were adjusted for age, smoking status, ER status, and PR status. But, the article did not report if they adjusted for BMI and breast size.
Q6 - Were the groups/participants free of the outcome at the start of the study (or at the moment of exposure)?	Yes	Low	The patients did not present RD at the recruitment moment.
Q7 - Were the outcomes measured in a valid and reliable way?	Yes	Low	Skin reaction was evaluated using The Common Terminology Criteria for Adverse Events v3.0.
Q8 - Was the follow up time reported and sufficient to be long enough for outcomes to occur?	Yes	Low	The occurrence and severity of acute RD were determined at the end of radiotherapy.
Q9 - Was follow up complete, and if not, were the reasons to loss to follow up described and explored?	Yes	Low	The study included 119 patients. Because the DNA quality of 17 patients was poor, only 102 patients were genotyped in the current study.
Q10 - Were strategies to address incomplete follow up utilized?	Unclear	Moderate	It is not clear from the study whether only 444 patients who had a sufficient amount of DNA were included in the analysis. The study reports that 77 of the 446 patients included in the study had severe acute RD, but it does not report the degree of RD of the 2 missing patients.
Q11- Was appropriate statistical analysis used?	Yes	Low	The associations between polymorphisms and severe acute RD were estimated by odds ratios and their 95% confidence intervals, which were calculated by unconditional logistic regression. The ORs were adjusted for age, smoking status, estrogen receptor (ER) status, and progesterone receptor (PR) status. BMI and breast size did not considered as confounding factors.

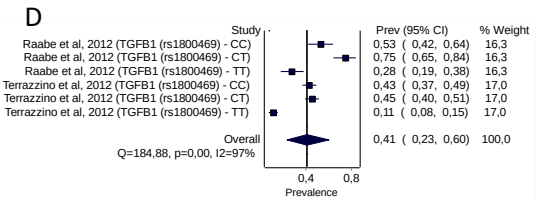
Legend: RT: Radiotherapy; PCR/RFLP: Polymerase Chain Reaction/Restriction Fragment Length Polymorphism; ER: Estrogen Receptor; PR: Progesterone Receptor; RD: Radiation Dermatitis; DNA: Deoxyribonucleic Acid; BMI: Body Mass Index.

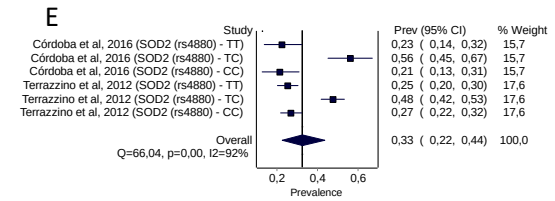
5.8.4. Appendix 4 - Prevalence meta-analysis of the SNPs in patients with breast cancer that developed RD: A) *XRCC3* (rs861539); B) *XPD* (rs1052559); C) *TP53* (rs1042522); D) *TGFβ1* (rs1800469); E) *SOD2* (rs4880); F) *GSTA1* (rs3957356); G) *MAD2L2* (rs2294638); H) *TGFβR3* (rs1926261); I) *OGG1* (rs2075747); J) *NEIL3* (rs3805169); K) *PTTG1* (rs3811999); L) *PTTG1* (rs2961950); M) *PTTG1* (rs2961952); N) *REV3L* (rs190246); O) *MAT1A* (rs2282367); P) *CD44* (rs8193); Q) *SH3GL1* (rs73234); R) *SH3GL1* (rs243336); S) *BAX* (rs918546); T) *GSTP1* (rs1695); U) *XRCC1* (rs1799782); V) *XRCC1* (rs25487).

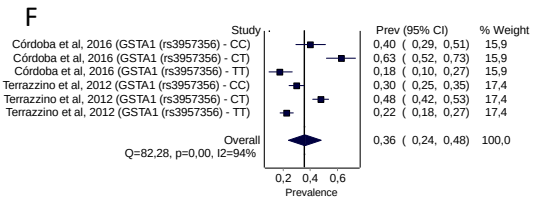


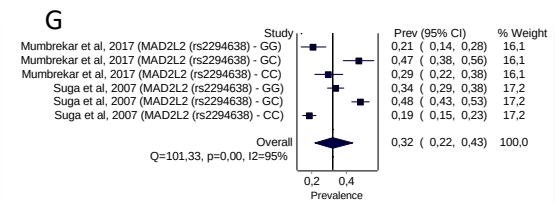


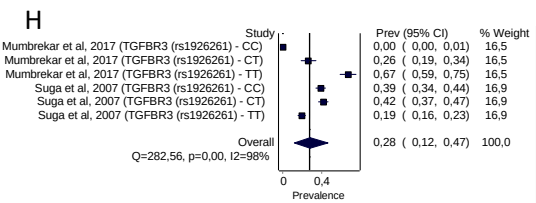












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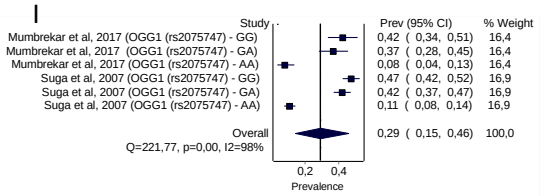

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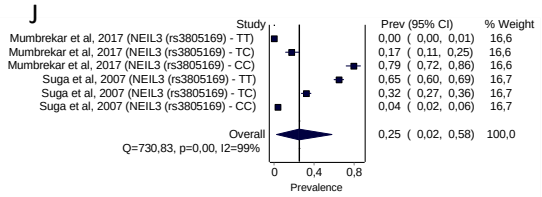

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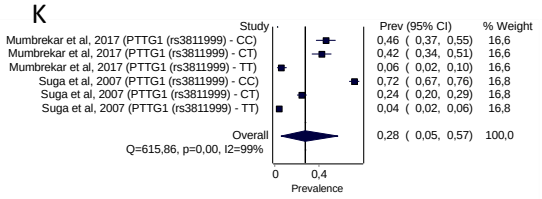

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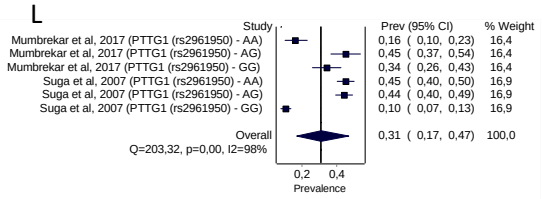

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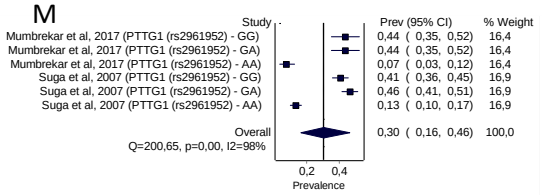

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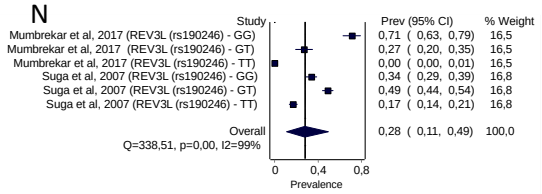

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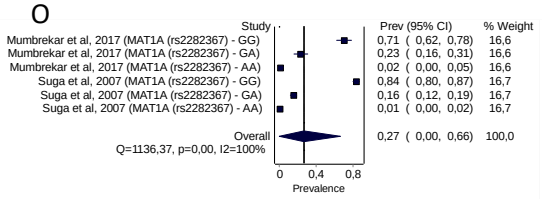

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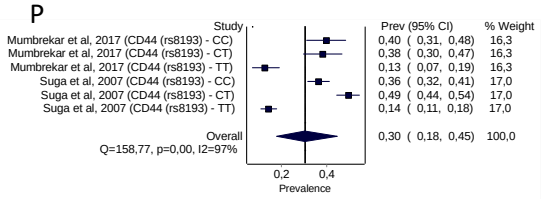

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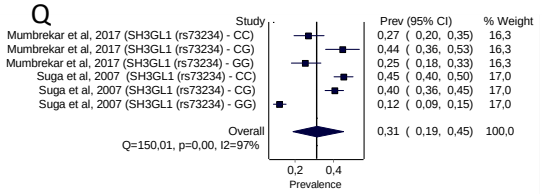

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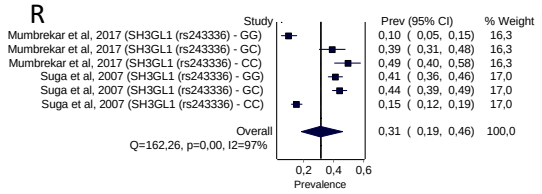

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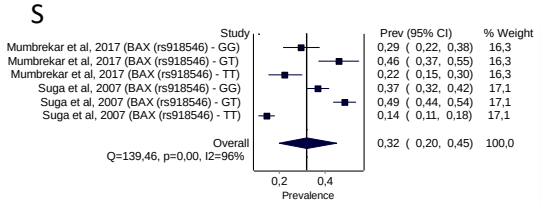

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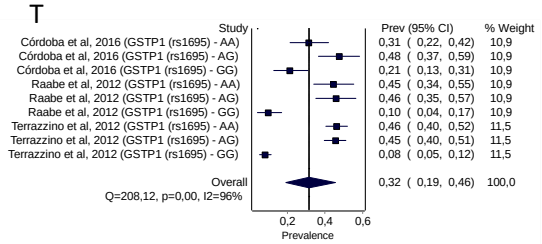

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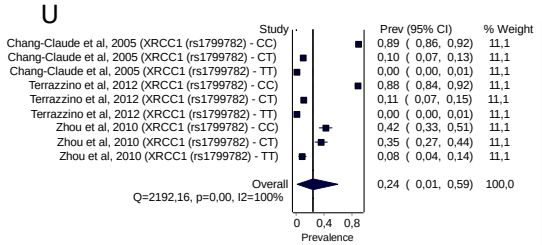

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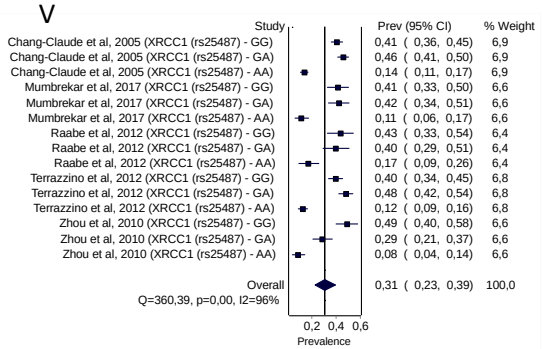
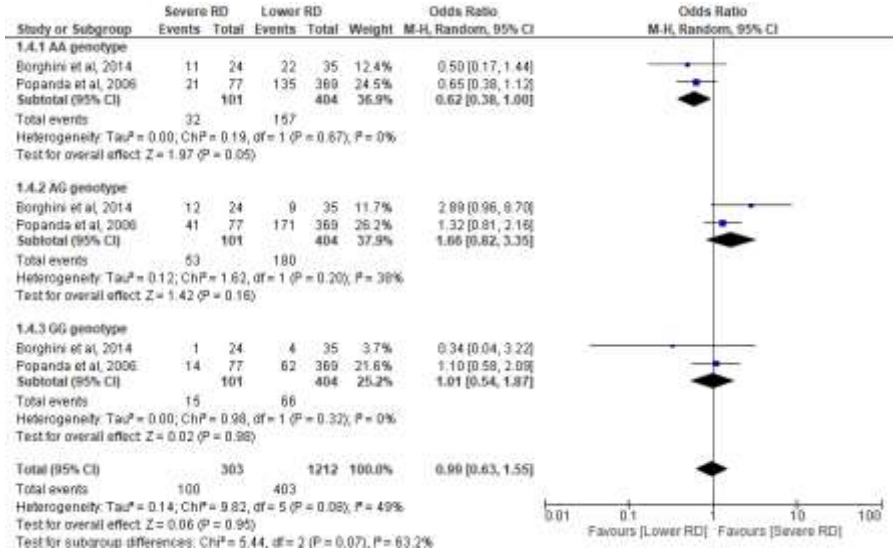
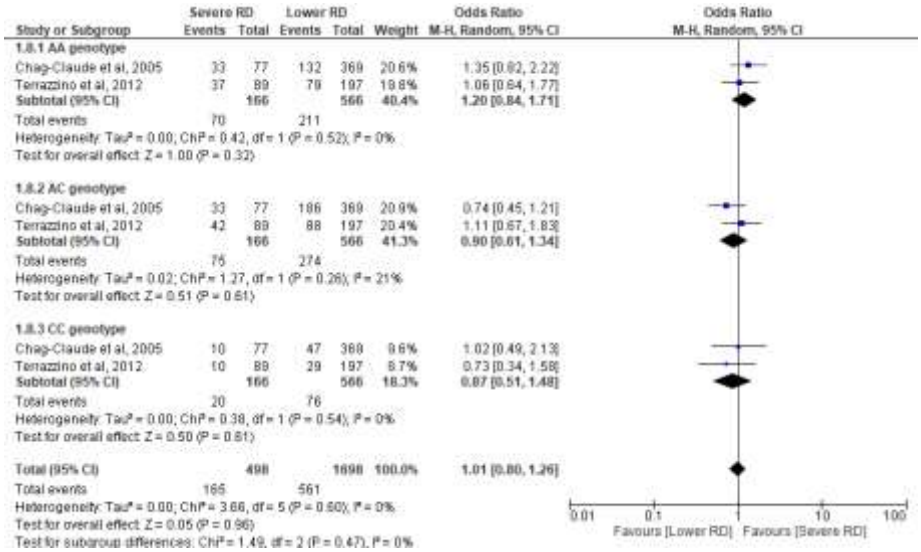


5.8.5. Appendix 5 - Association meta-analysis of the SNPs and RD severity with no statistical significance.

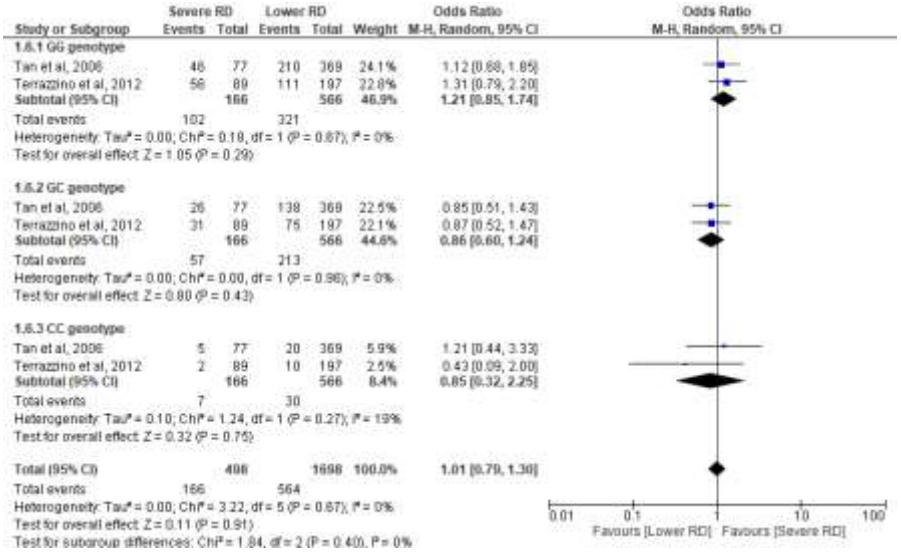
XRCC3 (rs861539)



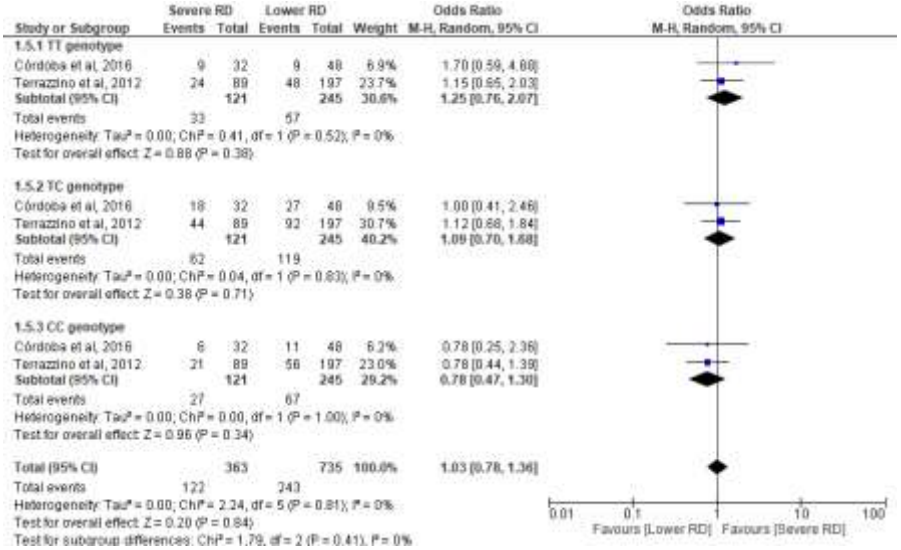
XPD (rs1052559)



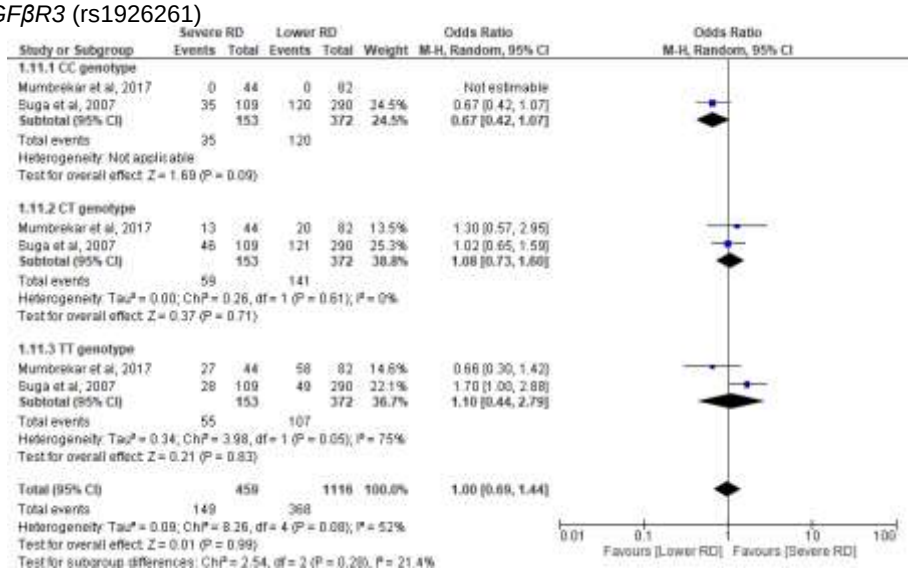
TP53 (rs1042522)



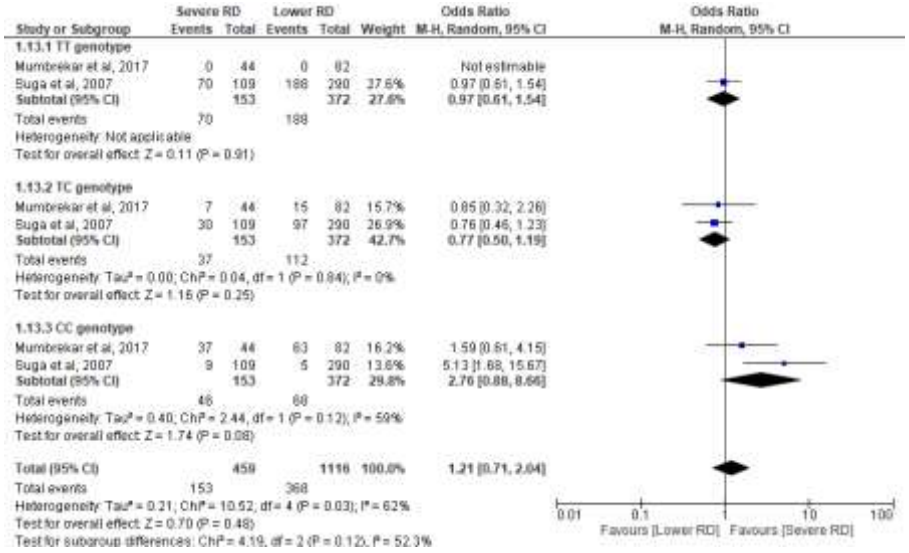
SOD2 (rs4880)



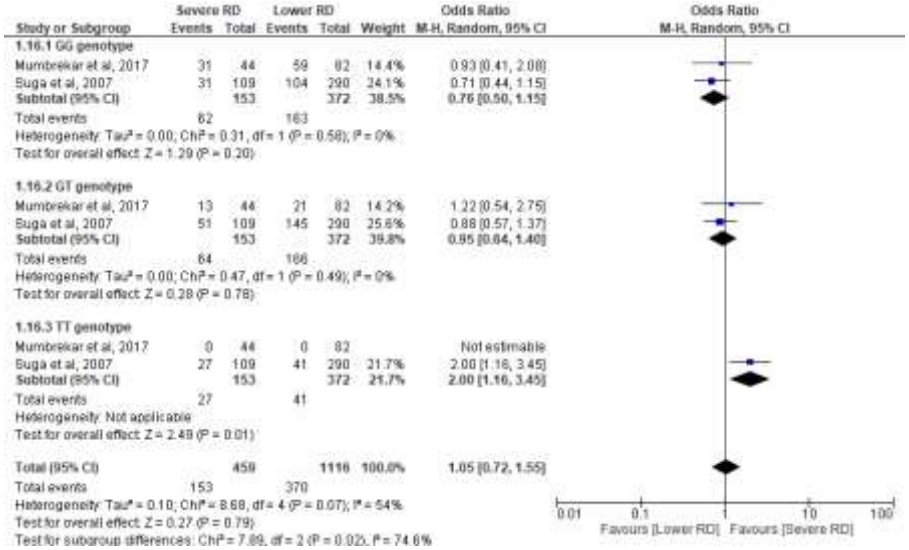
TGFβR3 (rs1926261)



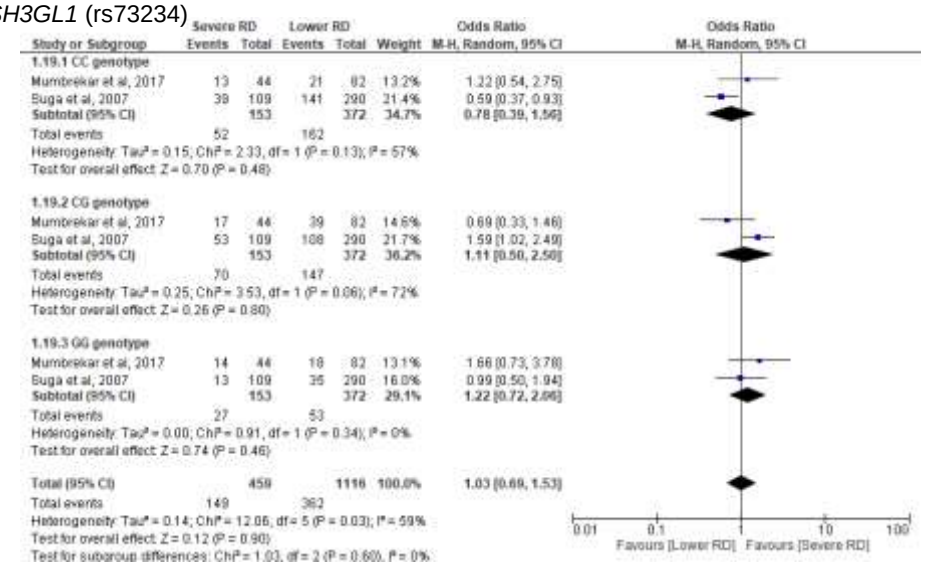
NEIL3 (rs3805169)



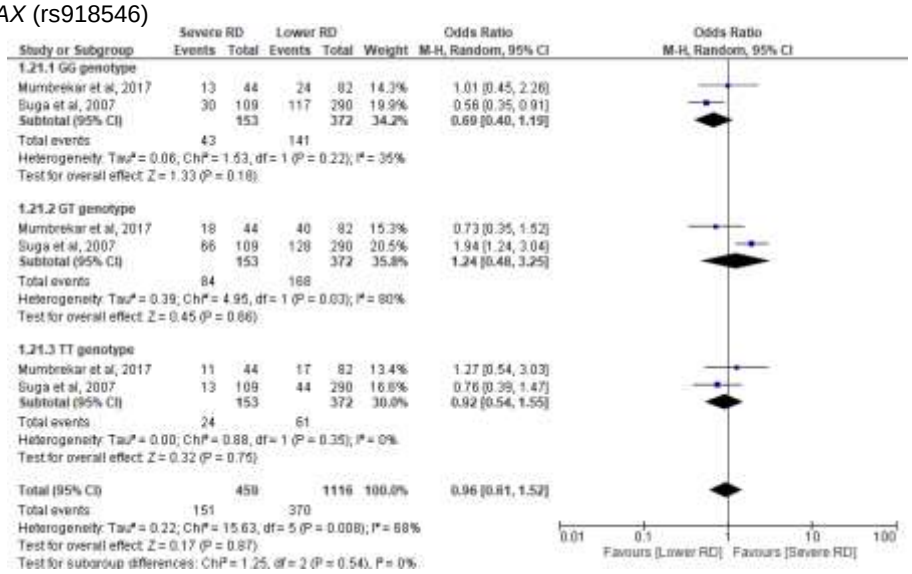
REV3L (rs190246)



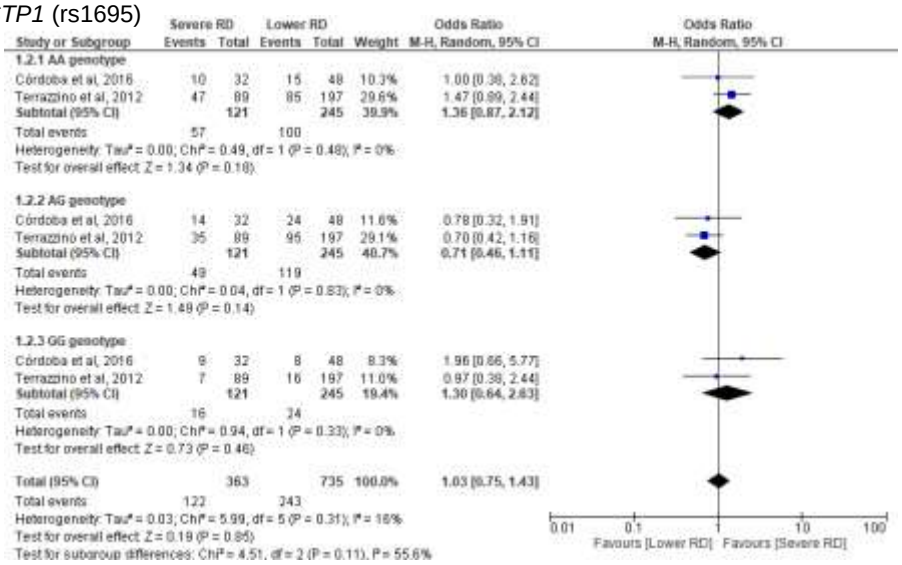
SH3GL1 (rs73234)



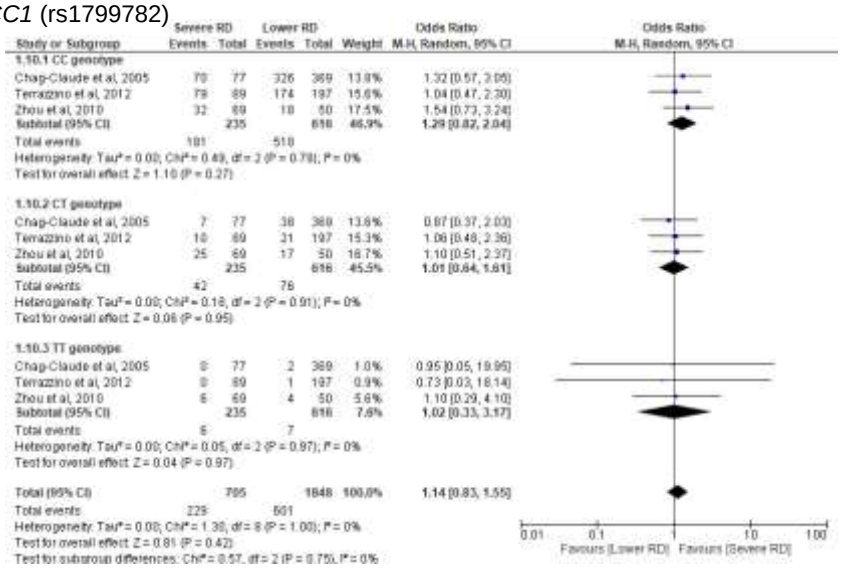
BAX (rs918546)



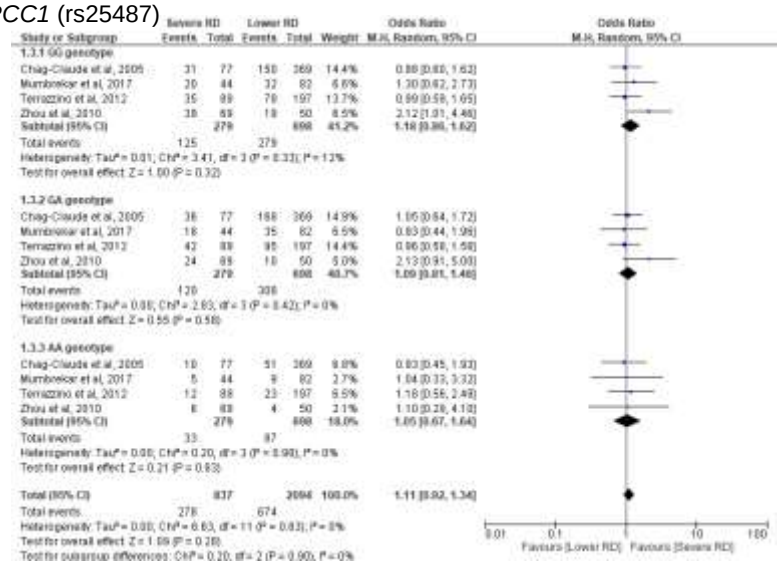
GSTP1 (rs1695)



XRCC1 (rs1799782)



XRCC1 (rs25487)



5.8.6. Appendix 6 - Certainty of evidence for association analysis accessed by Grading of Recommendation, Assessment, Development, and Evaluation (GRADE).

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
GSTA1 (rs3957356) - CC genotype												
2	observational studies	not serious	not serious	not serious	serious [a]	none	29/121 (24.0%)	72/245 (29.4%)	**OR 0.78** (0.47 to 1.29)	**49 fewer per 1.000** (from 130 fewer to 55 more)	⨁◯◯◯ VERY LOW	IMPORTANT
GSTA1 (rs3957356) - CT genotype												
2	observational studies	not serious	serious [b]	not serious	serious [a]	very strong association	62/121 (51.2%)	47/245 (19.2%)	**OR 5.57** (1.73 to 17.87)	**378 more per 1.000** (from 99 more to 617 more)	⨁⨁◯◯ LOW	IMPORTANT
GSTA1 (rs3957356) - TT genotype												
2	observational studies	not serious	not serious	not serious	serious [a]	none	31/121 (25.6%)	47/245 (19.2%)	**OR 1.49** (0.88 to 2.50)	**69 more per 1.000** (from 19 fewer to 181 more)	⨁◯◯◯ VERY LOW	IMPORTANT
GSTP1 (rs1695) - AA genotype												
2	observational studies	not serious	serious [c]	not serious	serious [a]	none	57/121 (47.1%)	100/245 (40.8%)	**OR 1.36** (0.87 to 2.12)	**76 more per 1.000** (from 33 fewer to 186 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
GSTP1 (rs1695) - AG genotype												
2	observational studies	not serious	not serious	not serious	serious [a]	none	49/121 (40.5%)	119/245 (48.6%)	**OR 0.71** (0.46 to 1.11)	**84 fewer per 1.000** (from 183 fewer to 26 more)	⨁◯◯◯ VERY LOW	IMPORTANT
GSTP1 (rs1695) - GG genotype												
2	observational studies	not serious	serious [d]	not serious	serious [a]	none	16/121 (13.2%)	24/245 (9.8%)	**OR 1.30** (0.64 to 2.63)	**26 more per 1.000** (from 33 fewer to 124 more)	⨁◯◯◯ VERY LOW	IMPORTANT
XRCC1 (rs25487) - GG genotype												
4	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	125/279 (44.8%)	279/698 (40.0%)	**OR 1.18** (0.86 to 1.62)	**40 more per 1.000** (from 36 fewer to 119 more)	⨁◯◯◯ VERY LOW	IMPORTANT
XRCC1 (rs25487) - GA genotype												
4	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	120/279 (43.0%)	308/698 (44.1%)	**OR 1.09** (0.81 to 1.46)	**21 more per 1.000** (from 51 fewer to 94 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
XRCC1 (rs25487) - AA genotype												
4	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	33/279 (11.8%)	87/698 (12.5%)	**OR 1.05** (0.67 to 1.64)	**5 more per 1.000** (from 38 fewer to 65 more)	⨁◯◯◯ VERY LOW	IMPORTANT
XRCC3 (rs861539) - AA genotype												
2	observational studies	not serious	not serious	not serious	serious [a]	none	32/101 (31.7%)	157/404 (38.9%)	**OR 0.62** (0.38 to 1.00)	**106 fewer per 1.000** (from 194 fewer to 0 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
XRCC3 (rs861539) - AG genotype												
2	observational studies	not serious	not serious	not serious	serious [a]	none	53/101 (52.5%)	180/404 (44.6%)	**OR 1.66** (0.82 to 3.35)	**126 more per 1.000** (from 48 fewer to 284 more)	⨁◯◯◯ VERY LOW	IMPORTANT
XRCC3 (rs861539) - GG genotype												
2	observational studies	not serious	serious [d]	not serious	serious [a]	none	15/101 (14.9%)	66/404 (16.3%)	**OR 1.01** (0.54 to 1.87)	**1 more per 1.000** (from 68 fewer to 104 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
SOD2 (rs4880) - TT genotype												
2	observational studies	not serious	not serious	not serious	serious [a]	none	33/121 (27.3%)	57/245 (23.3%)	**OR 1.25** (0.76 to 2.07)	**42 more per 1.000** (from 45 fewer to 153 more)	⨁◯◯◯ VERY LOW	IMPORTANT
SOD2 (rs4880) - TC genotype												
2	observational studies	not serious	serious [c]	not serious	serious [a]	none	62/121 (51.2%)	119/245 (48.6%)	**OR 1.09** (0.70 to 1.68)	**22 more per 1.000** (from 88 fewer to 128 more)	⨁◯◯◯ VERY LOW	IMPORTANT
SOD2 (rs4880) - CC genotype												
2	observational studies	not serious	not serious	not serious	serious [a]	none	27/121 (22.3%)	67/245 (27.3%)	**OR 0.78** (0.47 to 1.30)	**47 fewer per 1.000** (from 123 fewer to 55 more)	⨁◯◯◯ VERY LOW	IMPORTANT
TP53 (rs1042522) - GG genotype												
2	observational studies	not serious	not serious	not serious	not serious	none	102/166 (61.4%)	321/566 (56.7%)	**OR 1.21** (0.85 to 1.74)	**46 more per 1.000** (from 40 fewer to 128 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
TP53 (rs1042522) - GC genotype												
2	observational studies	not serious	not serious	not serious	not serious	none	57/166 (34.3%)	213/566 (37.6%)	**OR 0.86** (0.60 to 1.24)	**35 fewer per 1.000** (from 111 fewer to 52 more)	⨁⨁◯◯ LOW	IMPORTANT
TP53 (rs1042522) - CC genotype												
2	observational studies	not serious	serious [d]	not serious	serious [a]	none	7/166 (4.2%)	30/566 (5.3%)	**OR 0.85** (0.32 to 2.25)	**8 fewer per 1.000** (from 35 fewer to 59 more)	⨁◯◯◯ VERY LOW	IMPORTANT
PTTG1 (rs3811999) - CC genotype												
2	observational studies	serious [e]	not serious	not serious	not serious	none	111/153 (72.5%)	234/372 (62.9%)	**OR 1.75** (1.13 to 2.70)	**119 more per 1.000** (from 28 more to 192 more)	⨁◯◯◯ VERY LOW	IMPORTANT
PTTG1 (rs3811999) - CT genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	none	33/153 (21.6%)	117/372 (31.5%)	**OR 0.55** (0.35 to 0.87)	**113 fewer per 1.000** (from 176 fewer to 29 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
PTTG1 (rs3811999) - TT genotype												
2	observational studies	serious [e]	very serious [d,f]	not serious	very serious [a,g]	none	6/153 (3.9%)	16/372 (4.3%)	**OR 1.02** (0.16 to 6.58)	**1 more per 1.000** (from 36 fewer to 185 more)	⨁◯◯◯ VERY LOW	IMPORTANT
XPD (rs1052559) - AA genotype												
2	observational studies	not serious	not serious	not serious	not serious	none	70/166 (42.2%)	211/566 (37.3%)	**OR 1.20** (0.84 to 1.71)	**44 more per 1.000** (from 40 fewer to 131 more)	⨁⨁◯◯ LOW	IMPORTANT
XPD (rs1052559) - AC genotype												
2	observational studies	not serious	serious [d]	not serious	not serious	none	75/166 (45.2%)	274/566 (48.4%)	**OR 0.90** (0.61 to 1.34)	**26 fewer per 1.000** (from 120 fewer to 73 more)	⨁◯◯◯ VERY LOW	IMPORTANT
XPD (rs1052559) - CC genotype												
2	observational studies	not serious	serious [d]	not serious	serious [a]	none	20/166 (12.0%)	76/566 (13.4%)	**OR 0.87** (0.51 to 1.48)	**15 fewer per 1.000** (from 61 fewer to 52 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
MAD2L2 (rs2294638) - GG genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	none	60/153 (39.2%)	100/372 (26.9%)	**OR 1.86** (1.24 to 2.78)	**137 more per 1.000** (from 44 more to 237 more)	⨁◯◯◯ VERY LOW	IMPORTANT
MAD2L2 (rs2294638) - GC genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	none	63/153 (41.2%)	187/372 (50.3%)	**OR 0.69** (0.47 to 1.02)	**92 fewer per 1.000** (from 181 fewer to 5 more)	⨁◯◯◯ VERY LOW	IMPORTANT
MAD2L2 (rs2294638) - CC genotype												
2	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	29/153 (19.0%)	82/372 (22.0%)	**OR 0.79** (0.49 to 1.28)	**38 fewer per 1.000** (from 99 fewer to 45 more)	⨁◯◯◯ VERY LOW	IMPORTANT
XRCC1 (rs1799782) - CC genotype												
3	observational studies	not serious	not serious	not serious	not serious	none	181/235 (77.0%)	518/616 (84.1%)	**OR 1.29** (0.82 to 2.04)	**31 more per 1.000** (from 28 fewer to 74 more)	⨁⨁◯◯ LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
XRCC1 (rs1799782) - CT genotype												
3	observational studies	not serious	serious [d]	not serious	serious [a]	none	42/235 (17.9%)	76/616 (12.3%)	**OR 1.01** (0.64 to 1.61)	**1 more per 1.000** (from 41 fewer to 61 more)	⨁◯◯◯ VERY LOW	IMPORTANT
XRCC1 (rs1799782) - TT genotype												
3	observational studies	not serious	serious [d]	not serious	serious [a]	none	6/235 (2.6%)	7/616 (1.1%)	**OR 1.02** (0.33 to 3.17)	**0 fewer per 1.000** (from 8 fewer to 24 more)	⨁◯◯◯ VERY LOW	IMPORTANT
TGFβR3 (rs1926261) - CT genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	none	59/153 (38.6%)	141/372 (37.9%)	**OR 1.08** (0.73 to 1.60)	**18 more per 1.000** (from 71 fewer to 115 more)	⨁◯◯◯ VERY LOW	IMPORTANT
TGFβR3 (rs1926261) - TT genotype												
2	observational studies	serious [e]	very serious [b,d]	not serious	serious [a]	none	55/153 (35.9%)	107/372 (28.8%)	**OR 1.10** (0.44 to 2.79)	**20 more per 1.000** (from 137 fewer to 242 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
OGG1 (rs2075747) - GG genotype												
2	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	73/153 (47.7%)	168/372 (45.2%)	**OR 1.16** (0.72 to 1.87)	**37 more per 1.000** (from 79 fewer to 155 more)	⨁◯◯◯ VERY LOW	IMPORTANT
OGG1 (rs2075747) - GA genotype												
2	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	67/153 (43.8%)	146/372 (39.2%)	**OR 1.11** (0.57 to 2.16)	**25 more per 1.000** (from 123 fewer to 190 more)	⨁◯◯◯ VERY LOW	IMPORTANT
OGG1 (rs2075747) - AA genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	strong association	8/153 (5.2%)	45/372 (12.1%)	**OR 0.43** (0.19 to 0.99)	**65 fewer per 1.000** (from 95 fewer to 1 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
NEIL3 (rs3805169) - TC genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	none	37/153 (24.2%)	112/372 (30.1%)	**OR 0.77** (0.50 to 1.19)	**52 fewer per 1.000** (from 124 fewer to 38 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
NEIL3 (rs3805169) - CC genotype												
2	observational studies	serious [e]	serious [f]	not serious	serious [a]	strong association	46/153 (30.1%)	68/372 (18.3%)	**OR 2.76** (0.88 to 8.66)	**199 more per 1.000** (from 18 fewer to 477 more)	⨁◯◯◯ VERY LOW	IMPORTANT
PTTG1 (rs2961950) - AA genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	none	67/153 (43.8%)	134/372 (36.0%)	**OR 1.56** (1.04 to 2.34)	**107 more per 1.000** (from 9 more to 208 more)	⨁◯◯◯ VERY LOW	IMPORTANT
PTTG1 (rs2961950) - AG genotype												
2	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	62/153 (40.5%)	172/372 (46.2%)	**OR 0.82** (0.50 to 1.36)	**49 fewer per 1.000** (from 162 fewer to 77 more)	⨁◯◯◯ VERY LOW	IMPORTANT
PTTG1 (rs2961950) - GG genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	none	22/153 (14.4%)	62/372 (16.7%)	**OR 0.73** (0.42 to 1.26)	**39 fewer per 1.000** (from 89 fewer to 35 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
PTTG1 (rs2961952) - GG genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	none	51/153 (33.3%)	166/372 (44.6%)	**OR 0.61** (0.41 to 0.91)	**117 fewer per 1.000** (from 198 fewer to 23 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
PTTG1 (rs2961952) - GA genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	none	78/153 (51.0%)	162/372 (43.5%)	**OR 1.36** (0.93 to 1.99)	**77 more per 1.000** (from 18 fewer to 170 more)	⨁◯◯◯ VERY LOW	IMPORTANT
PTTG1 (rs2961952) - AA genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	none	23/153 (15.0%)	38/372 (10.2%)	**OR 1.63** (0.92 to 2.86)	**54 more per 1.000** (from 7 fewer to 143 more)	⨁◯◯◯ VERY LOW	IMPORTANT
REV3L (rs190246) - GG genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	none	62/153 (40.5%)	163/372 (43.8%)	**OR 0.76** (0.50 to 1.15)	**66 fewer per 1.000** (from 158 fewer to 35 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
REV3L (rs190246) - GT genotype												
2	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	64/153 (41.8%)	166/372 (44.6%)	**OR 0.95** (0.64 to 1.40)	**13 fewer per 1.000** (from 106 fewer to 84 more)	⨁◯◯◯ VERY LOW	IMPORTANT
MAT1A (rs2282367) - GG genotype												
2	observational studies	serious [e]	not serious	not serious	not serious	strong association	133/153 (86.9%)	290/372 (78.0%)	**OR 2.03** (1.18 to 3.48)	**98 more per 1.000** (from 27 more to 145 more)	⨁⨁◯◯ LOW	IMPORTANT
MAT1A (rs2282367) - GA genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	strong association	17/153 (11.1%)	74/372 (19.9%)	**OR 0.49** (0.27 to 0.87)	**90 fewer per 1.000** (from 136 fewer to 21 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
MAT1A (rs2282367) - AA genotype												
2	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	2/153 (1.3%)	3/372 (0.8%)	**OR 1.65** (0.12 to 23.68)	**5 more per 1.000** (from 7 fewer to 153 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
CD44 (rs8193) - CC genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	strong association	39/153 (25.5%)	156/372 (41.9%)	**OR 0.47** (0.31 to 0.71)	**166 fewer per 1.000** (from 236 fewer to 80 fewer)	⨁◯◯◯ VERY LOW	IMPORTANT
CD44 (rs8193) - CT genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	none	86/153 (56.2%)	159/372 (42.7%)	**OR 1.79** (1.22 to 2.63)	**145 more per 1.000** (from 49 more to 235 more)	⨁◯◯◯ VERY LOW	IMPORTANT
CD44 (rs8193) - TT genotype												
2	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	23/153 (15.0%)	50/372 (13.4%)	**OR 1.16** (0.68 to 1.97)	**18 more per 1.000** (from 39 fewer to 100 more)	⨁◯◯◯ VERY LOW	IMPORTANT
SH3GL1 (rs73234) - CC genotype												
2	observational studies	serious [e]	very serious [d,f]	not serious	serious [a]	none	52/153 (34.0%)	162/372 (43.5%)	**OR 0.78** (0.39 to 1.56)	**60 fewer per 1.000** (from 204 fewer to 111 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
SH3GL1 (rs73234) - CG genotype												
2	observational studies	serious [e]	very serious [d,f]	not serious	serious [a]	none	70/153 (45.8%)	147/372 (39.5%)	**OR 1.11** (0.50 to 2.50)	**25 more per 1.000** (from 149 fewer to 225 more)	⨁◯◯◯ VERY LOW	IMPORTANT
SH3GL1 (rs73234) - GG genotype												
2	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	27/153 (17.6%)	53/372 (14.2%)	**OR 1.22** (0.72 to 2.06)	**26 more per 1.000** (from 36 fewer to 113 more)	⨁◯◯◯ VERY LOW	IMPORTANT
SH3GL1 (rs243336) - GG genotype												
2	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	39/153 (25.5%)	137/372 (36.8%)	**OR 0.73** (0.33 to 1.64)	**70 fewer per 1.000** (from 207 fewer to 120 more)	⨁◯◯◯ VERY LOW	IMPORTANT
SH3GL1 (rs243336) - GC genotype												
2	observational studies	serious [e]	not serious	not serious	serious [a]	none	77/153 (50.3%)	147/372 (39.5%)	**OR 1.58** (1.08 to 2.31)	**113 more per 1.000** (from 19 more to 206 more)	⨁◯◯◯ VERY LOW	IMPORTANT

Certainty assessment							№ of patients		Effect		Certainty	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Severe RD	Lower RD	Relative (95% CI)	Absolute (95% CI)		
SH3GL1 (rs243336) - CC genotype												
2	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	37/153 (24.2%)	85/372 (22.8%)	**OR 0.94** (0.59 to 1.51)	**11 fewer per 1.000** (from 80 fewer to 81 more)	⨁◯◯◯ VERY LOW	IMPORTANT
BAX (rs918546) - GG genotype												
2	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	43/153 (28.1%)	141/372 (37.9%)	**OR 0.69** (0.40 to 1.19)	**83 fewer per 1.000** (from 183 fewer to 42 more)	⨁◯◯◯ VERY LOW	IMPORTANT
BAX (rs918546) - GT genotype												
2	observational studies	serious [e]	very serious [b,d]	not serious	serious [a]	none	84/153 (54.9%)	168/372 (45.2%)	**OR 1.24** (0.48 to 3.25)	**54 more per 1.000** (from 168 fewer to 276 more)	⨁◯◯◯ VERY LOW	IMPORTANT
BAX (rs918546) - TT genotype												
2	observational studies	serious [e]	serious [d]	not serious	serious [a]	none	24/153 (15.7%)	61/372 (16.4%)	**OR 0.92** (0.54 to 1.55)	**11 fewer per 1.000** (from 68 fewer to 69 more)	⨁◯◯◯ VERY LOW	IMPORTANT

CI: Confidence interval; OR: Odds ratio. RD: Radiation Dermatitis. **Explanations**: a. Number of the events < 300; b. $I^2 > 50\%$ and $p \leq 0.05$; c. One study had OR= 1; d. There is divergence in the estimation of the effect of the studies; e. The outcome has one study with a moderate risk of bias; f. $I^2 > 50\%$; g. 95% IC of the effect estimate is larger.

6 CONSIDERAÇÕES FINAIS

O sequenciamento genético tem sido muito utilizado como ferramenta para identificar marcadores capazes de predizer condições de saúde e doença. SNPs são marcadores genéticos frequentes na população, muito utilizados em estudos de associação genótipo-fenótipo e que tem sido avaliados em estudos de radiogenômica. Identificar SNPs que possam predizer o desenvolvimento de RD aguda pode ajudar a oferecer planejamento de radioterapia personalizado e individualizado. Dessa forma, não só fatores clínicos e dosimétricos seriam considerados para o planejamento da radioterapia, mas também fatores genéticos.

Os estudos incluídos nessa revisão, no geral, tiveram baixo a moderado risco viés. No entanto, vários SNPs foram avaliados para verificar a associação com RD aguda em apenas um estudo, o que não possibilitou que todos eles fossem incluídos na metanálise. A prevalência dos SNPs em pacientes com câncer de mama que apresentaram RD variou de 24 a 41%, mas todos tiveram alta inconsistência ($I^2 \geq 92\%$ p= 0). Sete genótipos de SNPs foram significativos para chance de RD severa e cinco genótipos de SNPs foram significativos para chance de RD leve. No entanto, esses genótipos apresentaram baixa ou muito baixa certeza da evidência.

Por isso, recomendamos que estudos futuros com grandes amostras incluam esses genótipos, que foram estatisticamente significativos nesta revisão, nas coortes de associação entre SNPs e RD para que seja possível recomendar essa ferramenta na prática clínica.

7 CONCLUSÃO

Em suma nossos resultados demonstram que a genotipagem de SNPs pode ser uma estratégia promissora para a predição de RD em pacientes com câncer de mama. Isso possibilitaria tratamentos personalizados e individualizados. No entanto, existe baixa a muito baixa certeza da evidência de que esses SNPs são capazes de predizer a severidade de RD. Este trabalho contribui para sintetizar dados dos SNPs já avaliados para capacidade de predizer RD. É necessário que estudos futuros de SNPs para predizer RD em pacientes com câncer de mama incluam os genes que já apresentaram associação estatisticamente significativa e foram mais prevalentes neste estudo. Além disso, estudos com populações de diferentes etnias e localizações geográficas são necessários para avaliar os SNPs em várias populações.

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