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Genetic polymorphisms of PPAR genes and human cancers: evidence for gene–environment interactions

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ABSTRACT

Peroxisome proliferator-activated receptors (PPARs) are nuclear transcription factors that play a role in lipid metabolism, cell proliferation, terminal differentiation, apoptosis, and inflammation. Although several cancer models have been suggested to explain PPARs' involvement in tumorigenesis, however, their role is still unclear. In this review, we examined associations of the different PPARs, polymorphisms and various types of cancer with a focus on gene–environment interactions. Reviewed evidence suggests that functional genetic variants of the different PPARs may modulate the relationship between environmental exposure and cancer risk. In addition, this report unveils the scarcity of reliable quantitative environmental exposure data when examining these interactions, and the current gaps in studying gene–environment interactions in many types of cancer, particularly colorectal, prostate, and bladder cancers.

KEYWORDS

Peroxisome proliferator-activated receptor (PPAR); genetic polymorphism; cancer risk; gene–environment interaction (GxE); tumorigenesis

1. Introduction

Peroxisomes are single membrane-bound organelles, with a granular matrix, that are found in different types of animal and plant cells. Peroxisomes host diverse metabolic functions, including α- and β-oxidation of fatty acids, bile acid and phospholipid biosynthesis, cholesterol biotransformation, and detoxification of oxygen-based reactive metabolites.[1] Peroxisome proliferator-activated receptors (PPARs) are a family of nuclear transcription factors that acquired their name when the first discovered receptor in this group was shown to mediate peroxisome proliferation in rodents upon chemical exposure. PPARs are currently associated with a much wider range of systemic and cellular functions beyond their reported role when first discovered (Figure 1). These receptors mainly regulate cellular functions and gene expression based on an activation by a ligand. Following binding by an agonist, PPARs release histone deacetylase

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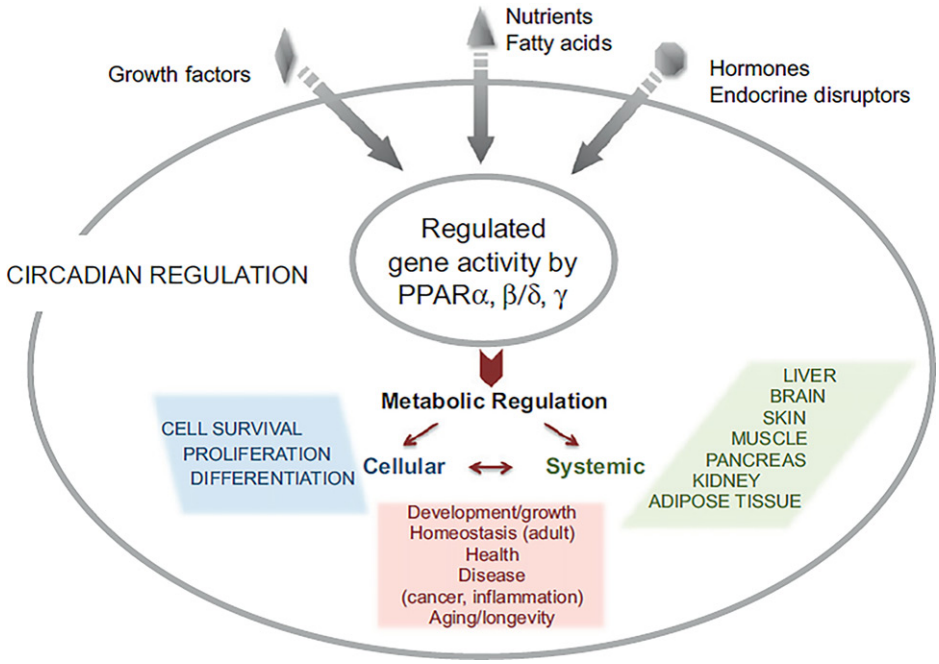

Figure 1. PPARs' physiological functions. Upon activation by different ligands, PPARs mediate a range of systemic and cellular metabolic pathways, including cell proliferation and differentiation, and various activities in a wide range of organs and tissues.[124]

(HDAC) co-repressors, hence enabling their hetero-dimerization with the retinoid X receptor (RXR). The RNA Polymerase II and the rest of the transcription machinery are then recruited to the forming complex in order to bind to PPAR responsive regulatory elements, known as direct repeat elements.[2,3] This mechanism underlies PPARs' involvement in the transcription of target genes that contribute to metabolism of hormones, carbohydrates, various lipids and general adipogenesis, as well as inflammatory responses, cell death, cell proliferation, and oncogenic signaling.[3] Whether a PPAR functions as an oncogene or as a tumor suppressor gene is still uncertain. This is mainly due to the complexity of the pathways that are regulated by PPARs, and their tendency to be altered in tumorigenesis in various types of cancer. The fact that PPARs are activated by both endogenous ligands and xenobiotics underlies their potential ability to regulate tumorigenesis dependently or independently of an environmental exposure.[4] In addition, their role in cancer-associated biological processes, including apoptosis, cell proliferation, and terminal differentiation, is still under research, with controversial results showing in many published reports.[3] Similarly, several studies and systematic reviews investigating an association between PPARs' polymorphisms and cancer risk are also showing inconsistencies.[5–7] However, data on gene–environment interactions potentially underlying these associations remains largely unexamined

despite the fact that some studies have suggested PPARs as important factors at the interface between genes and the environment.[8] This review aims at comprehensively examining the existing evidence of gene–environment interaction (GxE) underlying PPARs genetic polymorphisms and their association with cancer risk.

2. Search strategy

A literature search using MEDLINE and PubMed databases was performed to identify published original articles, systematic reviews, and editorials that included an analysis of the association between the peroxisome-proliferator (PP) activated receptors and risk for various types of cancer. The following keywords were used during the search with variations in syntax appropriate for each database: "peroxisome-proliferator activated receptor", "PPAR", "cancer", "cancer risk", "tumor", and "polymorphism". Titles and abstracts of identified citations were then screened to assess relevance. Articles selected satisfied the following criteria: (1) study is in the field of PP activated receptor and cancer risk. (2) The study targets cancer patients either as a case-control, cohort, or cross-sectional design, as well as systematic reviews and meta-analyses. (3) PPAR polymorphisms are listed in the study. (4) The study is available in full-text English. Articles excluded from the study were duplicated publications as well as studies on benign or precancerous lesions or other similar indicators, and non-English full-text articles. In total, 50 articles were identified as eligible in consensus between both coauthors. Full-text for identified eligible studies were then retrieved and screened against inclusion criteria. The following data was abstracted from those studies: first author and year of publication, study design, study country, ethnicity, genotyping method, sample size and subgroups (cases vs. controls), type of targeted cancer, methods of chemical exposure assessment, PPAR gene(s) and polymorphism, statistical significance of associations, gene–environment interaction details, and odds ratio with 95% confidence interval when applicable.

3. PPAR types & functions

So far, the PPAR family consists of three isoforms that have been identified in mammalians: PPAR-α, PPAR-γ, and PPAR-δ (also referred to as PPAR-β/δ). These differ from each other in terms of their function, ligand specificities, and expression distribution[9] (Table 1). PPAR-α was the first to be identified in the group, and is crucial for maintaining lipid homeostasis. It is ubiquitously expressed, particularly in tissues that depend on fatty acid oxidation, including kidneys, intestines, heart, skeletal muscles, and adipocytes.[10] PPAR-β/δ, on the other hand, is expressed mainly in the colon, skin, and intestinal epithelia,[11] and was detected in other tissues in humans

Table 1. PPARs physiological roles and patterns of expression in tissues and tumors

Gene	Tissue of expression	Physiological role	Expression patterns in tumors
PPAR-α	• Brown adipose tissue • Liver • Heart • Kidneys • Intestine	• Activates fatty acid and cholesterol catabolism, and stimulates gluconeogenesis and ketone body synthesis • Stimulates heme synthesis • Controls amino acid metabolism and urea synthesis • Reduces insulin resistance	• Low expression in gliomas[110] • Low expression in breast cancer[111]
PPAR-β/δ	• Skin • GI • Adipose tissue • Skeletal muscle • Brain • Placenta	• Controls energy homeostasis, fatty acid catabolism, and adaptive thermogenesis • Controls cell proliferation and terminal differentiation • Inhibits inflammation • Plays a role in placenta and GI development	• Has a broad expression distribution • Levels of expression depend on the extent of cell proliferation and differentiation • Low protein expression in tumors in quantitative studies[28] • Overexpressed in colon cancer[112]
PPAR-γ	*PPARγ1* • GI • Brain • Vascular cells • Immune Cells *PPARγ2* • Adipose tissues	• Regulates adipogenesis and lipid biosynthesis • Maintains lipid storage in white adipose and energy dissipation in brown adipose tissue • Reduces insulin resistance • Promotes differentiation of adipocytes • Plays a role in placenta and embryonic heart development	• Overexpressed in testicular cancer[125] • Overexpressed in ovarian, prostate, and breast carcinomas[113]

and animal models. PPAR-β/δ mainly regulates sugar and lipid homeostasis. Compared to the other two nuclear receptors, PPAR-β/δ has a relatively larger ligand-binding pocket enabling it to bind a wide range of endogenous substances and xenobiotics.[12] It can also inhibit inflammation triggered by a chemical stimulus, partially by the trans-repression of NFκB-dependent signaling, resulting in reduced cytokines expression. Activating PPAR-β/δ can also promote terminal cell differentiation in intestinal epithelium, keratinocytes, osteoblasts, and oligodendrocytes.[13] The third receptor in this class, PPAR-γ, is expressed in the spleen, the large intestine, and both white and brown adipose tissues.[2] Because the coding gene has separate promoters, the physiological role of PPAR-γ is mainly mediated by PPARγ1 and PPARγ2, which are derived from four different mRNAs.[14] PPAR-γ plays a key role in the regulation of adipogenesis, lipid biosynthesis, and maintaining cellular energy (Table 1). It is also involved in macronutrient metabolism, lipoprotein metabolism, and insulin sensitivity.[9] In addition, PPAR-γ seems to be important during development, particularly as a regulator of the blood–placental barrier.[15]

In addition to endogenous substances derived from diet and/or fatty acids, PPARs may be differentially modulated by a wide variety of

xenobiotic ligands, collectively known as peroxisome-proliferators. A growing number of toxic substances with high-volume production have been shown to have a high affinity to various PPARs, resulting in a significant impact on human health. Toxic substances, as parent compounds or their metabolites, were actually found to be functional PPAR ligands. More specifically, many plasticizers, industrial solvents, and environmental pollutants, are reported to be PPAR ligands. For instance, organotins tributyltin and triphenyltin, phthalate monoesters, trichloroethylene metabolites, perfluoroalkyl acid derivatives, and brominated flame retardants were all found to activate PPAR-α and PPAR-γ.[15] These xenobiotic ligands may be activating PPARs by competing with endogenous substances or indirectly resulting in the generation of endogenous ligands.[16,17] On the other hand, studies on animal models have suggested that PPARs are able to regulate expression of drug-metabolizing enzymes (DMEs).[18,19] Among regulated DMEs are epoxide hydrolases, aldehyde dehydrogenases, and the ubiquitous Phase I oxidation cytochrome P450 enzymes CYP2A, CYP2B, CYP2C, CYP2E1, and CYP3A.[20,21] In addition, PPARs are capable of directly impacting Phase II DMEs, although underlying mechanisms remain unclear. Earlier evidence suggested that PPARs' are able to regulate expression of Phase II enzymes glutathione-*S*-transferases (GSTs)[22] and UDP-glucuronosyltransferase 1A9 gene[23] via a functional response element in their promoter region.

4. PPARs' role in carcinogenesis

PPARs' expression levels vary in different types of tumors, including lung, endometrial, ovarian, breast, and other cancer types[5,24] (Table 1). In parallel, PPAR ligands are thought to be associated with a number of adverse effects including reproductive and developmental toxicity, neurological disorder, hepatic and cardiac injuries, and most importantly carcinogenicity.[25] However, the role of PPARs in carcinogenesis is still controversial.[26] The source of controversy is mainly based on evidence that PPARs and their ligands may act either as cancer promoters or as anti-tumorigenic factors, depending on tissue types and ligands' concentrations.[27] So far, four PPAR-mediated tumorigenic mechanisms have been proposed, including: (1) sustaining oxidative stress via generation of reactive oxygen species (2) inducing cell proliferation, (3) inhibiting apoptosis and senescence, and (4) promoting angiogenesis.[28–30]

Reddy et al. 1980 was the first study to show that chronic exposure to PPAR-α agonists causes liver cancer in rodents.[31] While the mechanism of action of hepatocarcinogenicity has been determined in mice, it was not evident in humans. In addition, many PPAR ligands were identified to be

non-genotoxic carcinogens, inducing hepatic tumors in rodents.[32] The mouse PPARα-dependent downregulation of the let-7c microRNA –which normally suppresses multiple oncogenic growth signaling pathways including JAK, STAT3, and c-Myc – appears to promote cancer development (Figure 2).[33] At the same time, a number of PPAR-α ligands were associated with the "tumor triad" effect which results in three types of cancer observed in rats, in the liver, the pancreas, and the Leydig cells.[10,34] Conversely, it is postulated that the anti-proliferative and anti-inflammatory properties of other PPAR-α agonists makes them promising chemopreventive and chemotherapeutic cancer drugs.[35] Hence different agonists may have different effects on tumor progression depending on the type of tissue and PPARα ligand.

The first evidence proposing that PPAR-β/δ promotes colon cancer was observed *in vitro* when the adenoma polyposis colitis tumor suppressor gene (APC) was found to suppress PPAR-β/δ expression.[36] However, later studies suggested that mutant APC may or may not lead to increased expression of PPARβ/δ and other drivers of cell proliferation.[37] Currently, two cancer models are suggested for PPAR-β/δ (Figure 2). In the first model, unknown endogenous ligands activate PPAR-β/δ, promote terminal differentiation, cause cell cycle arrest, and suppress inflammation. Consequently, the observed downregulation of PPAR-β/δ in different tumors causes deregulation in terminal differentiation and unleashes inflammatory signaling, hence increasing cell proliferation, inhibiting apoptosis, and ultimately resulting in tumor development.[28] In the second model, the expression of PPAR-β/δ in tumors is promoted through undefined mechanisms – possibly via APC–β-catenin-dependent signaling observed in several types of cancer. In this model, activation of PPAR-β/δ by unidentified ligands modulates the expression of a number of oncogenes – possibly including the vascular endothelial growth factor (VEGF) – which upregulates AKT phosphorylation, and therefore, inhibits apoptosis and promotes tumorigenesis. More specifically, agonists of PPAR-β/δ may promote tumor development, as well as inflammation, by inducing cyclin D1, IL-8, VEGF, and COX-2 expression.[4] Alternatively, unidentified target genes involved in cell cycle regulation could be upregulated by the overexpression of PPAR-β/δ in tumors.

The function of PPAR-γ in tumor development has also been explored, but rather more extensively than the other two receptors; however, it remains somewhat ambiguous. PPAR-γ agonists may regulate tumor progression in a dependent or independent manner, via inhibition of NFκB, c-Myc, Bcl2, VEGF, bFGF, and STAT3 (Figure 2).[38] *In vitro* studies showed that activation of PPAR-γ upregulates tumor suppressor pathways, including CDK inhibitors and PTEN, controls cancer invasiveness by

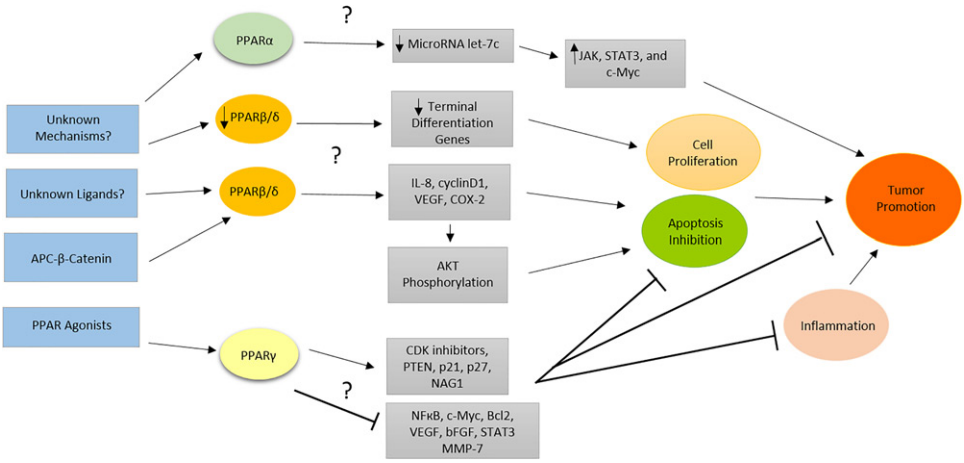

Figure 2. Suggested models for the role of PPARs in tumorigenesis. PPAR-α promotes tumorigenesis by downregulating microRNA let-7c. PPAR-β/δ can promote tumorigenesis by downregulating terminal differentiation genes or by promoting cell proliferation and blocking apoptosis via induction of cyclin D1, IL-8, VEGF, and COX-2 expression. PPAR-γ may regulate tumor progression in an agonist-dependent or independent manner, potentially involving inhibition of NFκB, c-Myc, Bcl2, VEGF, bFGF, STAT3, or upregulation of tumor suppressor pathways.

downregulating MMP-7, and promotes apoptosis by downregulating Bcl-2.[39] In addition, PPAR-γ is thought to suppress angiogenesis by inhibiting VEGFR and TGFβ-induced epithelial–mesenchymal transition in cancer cells.[40] This results in attenuation of MMPs secretion, invasiveness, and tumorigenic morphological changes. Other studies concluded that activating PPAR-γ prevents colon, breast, prostate and lung cancers.[10] In support, an earlier study on 470 patients with colorectal cancer (CRC) reported that patients with tumors overexpressing PPAR-γ showed lower cancer-specific mortality (adjusted HR: 0.44; $P = 0.0054$).[41] More recently, an epigenetic study in 116 subjects, including 70 CRC patients, revealed that hypermethylation of the PPAR-γ gene promoter is associated with a higher CRC risk.[42] Another PPAR-γ cancer model postulates that PPAR-γ agonists may inhibit cell proliferation, promote apoptosis, and trigger terminal differentiation through an unclear mechanism involving increased expression of both p21 and p27, as well as the non-steroidal anti-inflammatory drug-activated gene 1 (NAG1) and caveolin proteins.[28] The extent to which these events take place is dictated by the chemical structure of each PPAR-γ ligand and its affinity to the receptor.[43] However, the suggested cancer models are challenged by some studies reporting that activating PPAR-γ promotes tumorigenesis.[28]

In summary, although the PPAR-β/δ-null mouse model showed strong *in vivo* evidence of a role of PPAR receptors in development and cell proliferation,[44] however, so far, studies that convincingly proved a clear association between exposure to PPAR ligands and carcinogenicity are still

inconclusive, particularly in humans. It is important to consider that a ligand that activates a PPAR, may at the same time cause toxicity through other mechanisms of action. Ligand-induced toxicity may take place by receptor-independent events, or by both PPAR-dependent and PPAR-independent mechanisms.[45] Additionally, if/when a PPAR mediates an adverse effect, genetic polymorphisms of that PPAR need to be examined as they may be significant effect modifiers. Further, like most transcription factors, PPARs may be influenced by epigenetic regulators, which may modify ligand-mediated transcription and gene expression pathways. Epigenetic mechanisms, such as histone acetylation, DNA methylation, and miRNAs, may promote or inhibit the transcription of various PPARs by governing their mRNA translation or breakdown. Recently, a zinc-finger protein was identified among a group of unidentified transcription factors bound to the PPAR-γ gene non-methylated promoter.[46] Following an unknown trigger, the promoter gets hypermethylated, enriched in H3K9me2 & 3, and H3K27me3, then followed by binding a repressive complex, including DNMT2b, HDAC1, EZH2, and other components, ultimately resulting in repression of transcription. In addition, posttranslational modifications (such as phosphorylation and ubiquitination), interactions with coactivators -such as PPARGCA, CBP-p300, and SCRC1- and corepressors -such as RIP140α, SMRTα- may also affect the transcriptional activity and stability of PPARs.[47] So far, very few studies have examined the contribution of these mechanisms to PPAR-mediated cancer risk.

5. PPARs' genetic polymorphisms

PPARs have been shown to be genetically polymorphic. Two different isoforms have been reported for PPAR-α in diverse species including humans: PPARα1 and PPARα2, mapped to chromosome 22, adjacent to region 22q12-q13.1.[48] PPARα2 is truncated at exon 6, with no ligand-binding domain in the gene product, and hence is unable to bind any ligand. For PPARα1, The focus of the literature has mainly been on the rs1800206 (L162V) missense polymorphism, which results in a leucine to valine substitution at exon 5-codon 162 and a subsequent C > G substitution in the DNA-binding domain. Studies reported that the V162 allele encodes a higher transcription activity as compared to the L162 allele.[49] The L162V heterozygous genotype (CG) prevalence was reported to be 30% in Chinese,[5] 10.3% in US Caucasians,[50,51] and 3% among populations of African descent.[50]

On the other hand, the PPAR-β/δ gene, located on chromosome 6p21.2-p21.1, also shows multiple polymorphisms in introns, and in the following 5′- and 3'- untranslated regions (UTR): A65G (Asn163Asn: rs2076167) in

exon 7, and T-48444C (rs6902123) and T-842C (rs2267668) in exon 3.[52] An additional 5′-UTR polymorphism at +294T/C captured interest as it was suspected to alter binding of the SP1 transcription factor, while carriers of the minor C allele showed a higher transcriptional activity as compared to the T allele carriers.[53] Other polymorphisms are in high linkage disequilibrium with variations within the 3′- UTR, and may be considered as genetic markers for phenotypes of other SNPs in linkage disequilibrium.[54]

The human PPAR-γ gene, which is located on chromosome 3 at position 3p25, encodes 4 mRNAs based on alternate splicing or transcription of separate promoters.[55] Two isoforms γ1 and γ3 result in the same protein, while the third (γ2) varies with 28 amino acids extra and 5–6-fold increase in its ligand-dependent activating function.[56] As for PPARγ4, its localization is still not clearly defined. The PPAR-γ gene has a commonly reported missense C > G mutation in exon B (codon12), which results in a proline to alanine (Pro12Ala) substitution in the protein.[57] This Pro12Ala polymorphism causes a conformational change thought to be associated with a decreased transcriptional activity and a weaker transactivation of responsive promoters.[58] However, its association with cancer risk is still an area of controversy.[6] The Pro12Ala (CG) heterozygous genotype seems to be have a relatively higher prevalence in Caucasians compared to other ethnic groups; its prevalence was reported to be 28.7% in Finnish,[59] 18% in Italians,[60] and 19% in US Caucasian populations,[61] while it was found to be at 18.1% in a small Iranian population,[62] 11.7% in a Brazilian population,[63] 9.8% in aboriginal Arabs in Qatar,[64] and 9.7% in a Chinese population.[65] Other variants have been found to be in strong linkage disequilibrium with the Pro12Ala polymorphism, including the rs10865710 (C-681G), which resides in the promoter region, affecting gene regulation, as well as modulating the binding of transcription factor STAT5.[66] Another identified PPAR- γ polymorphism is the His477His, which results in a silent substitution of histidine residue at exon 6 (C161T/C1431T; rs3856806).[67]

6. PPARs' polymorphism and associated cancer risk

In recent years, more studies reported on the role of genetic susceptibility in cancer risk with distinct patterns in low-penetrance genes among cancer patients from different ethnic groups.[68] As a low-penetrance gene, functional genetic variations in PPAR may have a subtle effect on individual cancer risk. However, this effect may significantly impact the population disease burden if a "high-risk" polymorphism has a significant prevalence in the population, and/or a GxE is underlying an excessive environmental exposure; in cases of a GxE, cancer risk associated with a particular

environmental stressor changes with different functional polymorphisms. As part of this review, we examined recent work on PPARs' genetic polymorphism and its association with cancer risk. Depicted inconsistency between the different studies may be explained by variations in sample size, over-reporting of positive associations in subgroups from datasets, unassessed exposures, and other unexamined genetic factors contributing to cancer risk. Yet, results do highlight a number of important observations based on the reported environmental and genetic data. First, studies examining PPARs' associations with cancer risk mostly focused on CRC and breast cancer, and to a lesser extent on gastric, prostate, and lung cancer (Table 2). Second, in breast cancer, PPAR-γ polymorphisms, including the most prevalent human polymorphism Pro12Ala, most likely do not have an independent effect on cancer risk since the weight of evidence points into absence of a statistically significant association.[69–74] No statistically significant associations were found for Pro12Ala polymorphism and breast cancer in studied US populations, either in a large group of nurses[74] or in a cohort of postmenopausal women living in Maryland.[73] Similar results were found in Asians, both in a Taiwanese female population[72] and in Koreans,[70] as was well as in Hispanic populations from Mexico.[69,71] In contrast, one study in Danish Caucasians reported a lower breast cancer risk for both the homozygous and heterozygous carriers of the Ala-allele variant,[75] while a more recent study in a Chinese group reported a significantly higher risk for carriers of the allele compared to homozygous wild-type.[5] On the other hand, a number of PPAR-α polymorphisms were found to be associated with breast cancer risk. An almost twofold breast cancer risk was found for carriers of the PPAR-α rs4253760 polymorphism in postmenopausal New Yorker women, showing evidence of a linear trend ($P = 0.02$),[51] and for carriers of the rs1800206 polymorphism in Chinese Han women.[5] In contrast, associations were not statistically significant for the same SNP (rs1800206) in the New Yorker group. Similarly, the PPAR-α V227A polymorphism (rs1800234) was not found to be associated with breast cancer risk in a Taiwanese female case-control group.[56] Therefore, the association between PPAR-α and breast cancer remains inconclusive. Conversely, carriers of the combined PPAR-γ rs1805192 and PPAR-α rs1800206 polymorphisms had the highest breast cancer risk as compared to combined homozygote wild-type carriers, even after adjustment for confounding covariates (OR, 2.59; 95% CI:1.70–3.48).[76]

On the other hand, evidence of associations in CRC are largely controversial. The fact that PPAR-γ Pro12Ala decreases transcriptional activity, suggests a weaker control of tumorigenic changes, and hence a higher cancer risk in carriers of that particular genetic variant. However, this is not clearly reflected in the reported studies. The PPAR-γ Pro12Ala

Table 2. Description of studies investigating PPARs' polymorphisms and associated cancer risk.

Gene	SNP	Cancer type	Country of study	Ethnic group	Study design	#Participants		Associations[b] (OR; 95%CI or *p*-value)	Study
						Cases	Controls (origin)[a]		
PPAR-α	rs135539 rs1800206	Breast	China	Asian	Case-control	432	430	NS S Higher risk (1.85; 1.31–2.47)	5
	rs1800234 (V227A)	Breast	Taiwan	Asian	Case-control	306	300 (HB)	NS	56
	rs135542 rs1800206 (L162V) rs4253623 rs4253699 rs4253755 rs4253760	Breast	USA	Mixed	Case-control	1,073	1,112	NS NS NS NS NS S Higher Risk (1.97; 1.14–3.43)	51
	rs1800206 (Leu162Val)	Lung	USA	Caucasian	Case-control	1,553	1,730 (HB)	S Higher risk (1.21; 1.04–1.42)	97
PPAR-β/δ	294T/C (rs2016520	Colorectal (CRC)	Mexico	Hispanic	Case-control	97	178	S Protective Among the T/C genotype carriers (0.39; 0.22–0.69)	89
	rs2076167 rs3734254	Gastric	China	Asian	Case-control	196	397 (PB)	S Higher risk among the GG variant carriers (2.20; 1.12–4.32) NS	93
	rs3734254	Lung Upper aero-digestive tract (UADT)	USA	Not specified	Cross-sectional	1212	–	S Protective (0.63; 0.42, 0.96) S Protective (0.51; 0.27–0.99)	95
	5′-UTR(T/C) (rs2016520)	Lung	USA	Caucasian	Case-control	1,553	1,730 (HB)	S Higher risk (1.21; 1.04–1.42)	97
PPAR-γ	Pro12Ala	Bladder	USA	Not specified	Case-control	465	450	S Protective among untreated patient carriers (0.41; 0.20–0.86)	101

rs1801282	Bladder	Pakistan	Indian	Case-control	200	200 (PB)	NS	114
rs1805192	Breast	China	Asian	Case-control	432	430	Higher risk (1.97; 1.42–2.53)	5
rs10865710							NS	
rs4684846	Breast	Korea	Asian	Case-control	456	461 (HB)	NS	70
rs1801282								
rs2120825								
rs2938395								
rs1175540								
rs3856806								
rs3856806								
Pro12Ala	Breast	Mexico	Hispanic	Case-control	197	220 (PB)	NS	69
Pro12Ala	Breast	Mexico	Hispanic	Case-control	208	220 (PB)	NS	71
rs10865710 (C681T)	Breast	Taiwan	Asian	Case-control	291	589 (HB)	NS	72
rs1805192 (Pro12Ala)							NS	
rs3856806 (C1431T)							NS	
Combined at-risk haplotypes							S	
C681T (CCT)+ Pro12Ala (GGT) + C1431T (GGC)							Higher risk (1.67;1.11–2.52)	
rs4684847 (IVS3-6622)	Breast	USA	Not specified	Cohort study	1,016 postmenopausal women		NS	73
rs709158 (IVS9 + 4523)					61	933		
rs1175543 (IVS9 + 7780)								
rs1801282 (Pro12Ala)								
Pro12Ala	Breast	USA	Mixed	Nested case-control	725	953	NS	74
Pro12Ala	Breast	Denmark	Caucasian	Nested case-control	361	361	S Protective for CG genotype carriers (0.66; 0.45–0.96)	75
rs1801282 C > G	Breast	–	–	Meta-analysis	3,931	5,382	NS	115
Pro12Ala	Breast	–	–	Meta-analysis	2,279	2,360	S Protective (0.84; 0.72–0.98)	116
Pro12Ala	CRC	India	Indian	Case-control	301	291 (HB)	NS	83

(*continued*)

Table 2. Continued.

Gene	SNP	Cancer type	Country of study	Ethnic group	Study design	#Participants Cases	#Participants Controls (origin)[a]	Associations[b] (OR; 95%CI or *p*-value)	Study
	C161T							S Higher risk among the C/T + T/T carriers (1.61; 1.10–2.36)	
	Pro12Ala	CRC	Singapore	Asian	Nested case-control	362	1,164 (PB)	S Protective among PPARγ-2 carriers (0.53; 0.30–0.92)	78
	Pro12Ala	CRC (colon) CRC (rectal)	USA	Mixed	Case-control	1577 794	1,971 (PB) 1,001 (PB)	NS S Higher risk among the PA/AA Phenotype carriers with a high mutagen index (1.63; 1.12–2.36)	84
	Pro12Ala	CRC	Spain	Spanish	Case-control	377	326 (HB)	S Protective (0.56; 0.37–0.85)	79
	Pro12Ala	CRC	–	–	Meta-analysis	4,533	6,483	S Protective in colon cancer patients only (OR = 0.80, $p = 0.040$)	80
	Pro I 2Ala	CRC	–	–	Meta-analysis	17,289	54,927	S Higher risk (1.498; 1.139–1.970)	77
	Pro12Ala	CRC	–	–	Meta-analysis	13,575	17,085	S Protective among the pooled sample (0.90; 0.83–0.98) S Protective among Caucasians (0.91; 0.83–0.99) NS among Asians	6

Pro12Ala	CRC	USA	Caucasian	Nested case-control	135	269 (PB)	NS	85
rs9858822	CRC	USA	Mixed	Case-control	2,152	2,630	S Higher risk (1.36; 1.16–1.60)	117
Pro12Ala	CRC	Korea	Asian	Case-control	701	1,402	NS	86
Pro12Ala	CRC	China	Asian	Case control	387	1,536	NS	81
Pro12Ala	CRC	–	–	Meta-analysis	12,761	21,113	S Protective among G carriers (0.92; 0.84–0.99)	
Pro12Ala (rs1801282)	CRC	–	–	Meta-analysis	14,451	18,013	S Protective in both rectal and colon cancer (0.82; 0.73–0.92)	82
His477His (rs3856806)							S Protective in pooled populations and among Caucasians (0.66; 0.44–1.00)	
Pro12Ala	CRC	Japan	Asian	Case-control (2 study groups)	128	238 (HB)	NS	87
C161T (rs3856806)					257	771 (HB)	NS	
Pro12Ala	Endometrial	USA	Mixed	Nested case-control	222	666 (PB)	NS	118
Pro12Ala	Esophageal cancer	China	Asian	Case-control	507	1,496	NS	94
rs10865710 rs1801282 rs3856806 rs13306747	Gastric	China	Asian	Case-control	196	397 (PB)	NS	93
Pro12Ala (rs1801282)	Gastric	Turkey	Turkish	Case-control	50	120 (HB)	S Higher risk (1.95; 1.58–2.40)	91
Pro12Ala	Gastric	Japan	Asian	case-control	215	201 (HB)	S (2.43; 1.04–5.67)	92

(*continued*)

Table 2. Continued.

Gene	SNP	Cancer type	Country of study	Ethnic group	Study design	#Participants		Associations[b] (OR; 95%CI or *p*-value)	Study
						Cases	Controls (origin)[a]		
	Pro12Ala	Gastric	–	–	Meta-analysis	546	827	S In variant G allele carriers [CG + GG]: Higher risk among pooled sample (2.31; 1.67–3.21) S Higher risk among Asians (2.56; 1.42–4.64) S Higher risk among Caucasians (2.20; 1.48–3.25)	119
	rs10865710 rs1801282 rs3856806 rs13306747	Upper aero-digestive tract (UADT)	USA	Not specified	Cross-sectional	1212	–	NS	95
	Pro12Ala (rs1801282)	Lung	USA	Caucasian	Case-control	1,553	1,730 (HB)	NS	97
	rs13073869 rs1899951 rs4135247 rs2028759 rs2972162 rs2938395 rs1151997 rs796313 rs709151 rs1175541 rs1175543	Lung	China	Asian	Matched case-control	500	517 (PB)	S Protective dominant model (0.65; 0.51–0.85) S Protective dominant model (0.58; 0.37–0.90) S Protective based on a log additive model (0.85; 0.71–1.01) NS S Protective based on an overdominant model 0.78 (0.60–1.00) NS NS	96

							NS S Protective based on an overdominant model (0.73; 0.57–0.94) S Protective based on an overdominant model (0.73; 0.57–0.94) S Protective based on an overdominant model (0.76; 0.59–0.98)	
c.1347C > T	Lung cancer Various types	China –	Asian –	Case-control Meta-analysis	521 6,814	1,030 14,590	NS S Higher risk among T carriers (1.11; 1.02–1.21)	120
rs1801282 C > G	Liver	China	Asian	Case-control	584	923 (HB)	S Protective among CG genotypes (0.47; 0.27–0.82) S Protective among GC + GG genotypes (0.52; 0.31–0.88) S Protective among G allele carriers (0.56;0.38–0.82)	121
rs3856806 C > T							S Higher risk among TT genotypes (2.33; 1.25–4.36) S Higher risk among T allele carriers (1.21; 1.02–1.44)	
Pro12Ala C161T	Melanoma	Germany	Caucasian	Case-control	832	790 (HB)	NS S	98

(*continued*)

Table 2. Continued.

Gene	SNP	Cancer type	Country of study	Ethnic group	Study design	#Participants Cases	#Participants Controls (origin)[a]	Associations[b] (OR; 95%CI or *p*-value)	Study
								Higher risk Among the T allele carriers (5.18; 1.68–15.96)	
	Pro12Ala	Ovarian	China	Asian	Case-control	687	687 (HB)	S Higher risk (1.52; 1.01–2.29)	122
	Pro12Ala	Pancreatic	USA	Mixed	Matched case-control	83	166	NS Higher risk (borderline significance: (1.79; 0.96–3.33)	100
	rs1801282 C > G	Pancreatic	Japan	Asian	Case-control	360	400	NS	123
	Pro12Ala	Prostate	Finland	Caucasian	Nested case-control	193	188 (PB)	NS	59
	Pro12Ala	Prostate	USA	Caucasian	Case-control	91	237 (PB)	NS	61
	Pro12Ala	Prostate	China	Asian	Case-control	543	753	NS	65
	Pro12Ala	Prostate	Denmark	Caucasian	Nested case-control	370	370 (PB)	NS	90
	Pro12Ala (rs1801282) His447His [C161T]	Various types	–	–	Meta-analysis	11,627 1,819	16,050 2,642	NS NS	88
	Pax8-PPARγ1 Rearrangement	Thyroid cancer	–	–	Meta-analysis	198	268	S Higher risk in carriers of the genetic rearrangement (6.63; 3.5–12.5)	7

[a]Origin of controls if specified by source: population-based (PB); hospital-based (HB).
[b]Associations: significant (S) at $p<0.05$; non-significant (NS); odds ratio (OR).

polymorphism was found to be significantly associated with a 50% higher CRC risk in only one study,[77] significantly protective in seven other studies in various ethnic groups and mixed study populations,[6,78–82] and non-significant in eight other studies (Table 2).[81,83–87] In meta-analysis reports in particular, three studies found the Pro12Ala polymorphism to be protective among a large pool of subjects including mixed populations, as well as among Caucasian subgroups,[6,80,88] while only one study reported it to be significantly associated with a 50% higher CRC risk.[77] Conflicting results in PPAR-γ penetrance were also found for the C161T polymorphism, while only one study examined PPAR-β/δ polymorphism in CRC and reported a protective effect for the 294T/C variant.[87,89] Therefore, the association between PPAR-γ and CRC risk also requires further examination based on the presented evidence.

At the level of prostate cancer, PPAR-γ Pro12Ala polymorphism's association with cancer risk was consistently non-significant in European and US Caucasians, as well as in Asians.[59,61,65,90] In contrast, studies in gastric cancer showed a 2-fold increased risk in carriers of the Pro12Ala polymorphism,[91,92] as well as in carriers of the PPAR-β/δ rs2076167 GC variant.[93] On the other hand, in three examined studies on lung cancer, PPAR-γ Pro12Ala polymorphism did not show a significant association with cancer risk, both in Caucasian and non-Caucasian populations. Similar results were reported in a study on esophageal cancer.[94] In contrast, some PPAR-β/δ variants, such as the rs20116520, were shown to be associated with a higher lung cancer risk, while others, such as the 3'-UTR rs3734254, which affects mRNA stability, was reported to have a protective role.[95–97] Studies in other types of cancer were too scarce, hence precluding us from identifying any patterns of associations.[80,98–101]

7. Evidence of gene–environment interactions

Among examined studies, only 14 reports investigated GxE interactions underlying cancer risk. A number of remarks can be made when reviewing extracted data. First, the assessed environmental exposure information included biomonitoring, such as urinary levels of arsenates and phthalates, data from medical records, and self-reported information based on direct interviews, such as smoking history, alcohol consumption, medication usage, and dietary habits. Second, for the common PPAR-γ Pro12Ala polymorphism, significant interactions with phthalate exposure, NSAIDs usage, as well as alcohol consumption are reported in breast cancer (Table 3). Carriers of the Pro12Ala variant with higher urinary levels of MEHHP phthalate showed a higher breast cancer risk compared to wild-type carriers.[71] In contrast, Pro12Ala had a protective effect in users of more than

two NSAID pills per month over a year in a Danish Caucasian group.[75] Among the same Caucasian group, homozygous wild-type carriers consuming more than 10 g alcohol/day had a 20% higher breast cancer risk compared to alcohol users carrying the variant allele; however, the variant genotype did not show a protective effect against breast cancer in alcoholics.[75] Similarly, Pro12Ala polymorphism had no effect on the association between arsenic urinary levels and breast cancer risk in a group of Mexican women.[69] Together, these findings do suggest that the PPAR-γ Pro12Ala polymorphism may interact with an environmental stimulus, however, its effect in modifying breast cancer risk depends on the stimulating agent and its mode of interaction. In support, many environmental chemicals have been recognized as PPAR-γ agonists, including phthalates.[15] Phthalates in particular were previously shown to activate the PPAR:RXR signaling for all 3 PPAR isoforms in a fish model.[102] In fact, a number of studies report findings that point in the direction of a GxE interaction, within the context of the reviewed evidence above. For instance, studies have indicated that chemicals of widespread human exposure, such as house dust and organotins, that may be present in drinking water, are actually activators of the PPAR-γ signaling pathway.[16,17] Evidently, the question of how a PPAR-γ genetic variant can modify the effect of such environmental exposures in initiating and promoting tumorigenesis is still not answered, and hence requires further mechanistic research. In lung cancer, carriers of the PPAR-γ rs1899951 A allele increased significantly with the smoking dose (measured in pack-years) compared to homozygote GG genotypes (GA/AA vs. GG).[96] However, this association in lung cancer was not observed for the PPAR-γ Pro12Ala polymorphism in two other groups of US Caucasians and Asians.[95,97] PPAR interaction was also not significant with alcohol, tobacco smoking, or diet in both gastric and colorectal cancer (Table 3).[78,91] In addition, in prostate cancer, the Pro12Ala variant did not modify the association between aspirin usage and prostate risk.[90] However, men with a high BMI carrying that variant had a higher prostate cancer risk; this suggests that PPAR-γ normally protects against prostate tumors, while in carriers of the Pro12Ala variant a decreased transcriptional activity may be attenuating protective mechanisms such as anti-apoptotic and anti-proliferative pathways.

On the other hand, carriers of the PPAR-β/δ missense GC variant rs2076167 having excessive dietary salt consumption had a 5-fold higher gastric cancer risk compared to non-carriers with similar dietary habits[93] (Table 3). In addition, in lung and UADT cancers, smokers carrying the PPAR-β/δ 3'-UTR polymorphism rs3734254 were protected compared to non-carrier smokers, whereas the 5'-UTR polymorphism rs2016520 did not show a statistically significant interaction in the same type of cancer.[95,97]

Table 3. Description of studies investigating gene–environment interactions underlying PPAR's polymorphism and cancer risk.

Gene	SNP	Cancer type	Ethnic group, country of study	Study design	#Participants		Environmental stimulus	GxE Interactions (OR;CI)	Comments	Study
					Cases	Controls (origin)[a]				
PPAR-α	rs4253623 rs4253699 rs4253755 rs4253760 rs135542 rs1800206	Breast	Mixed, USA	Case-control	1,073	1,112	Self-reporting on aspirin use defined as at least once/week for 6 months or more	Inverse associations with aspirin use among women with referent genotypes, and homozygous rs135542 No Interaction	PPAR-α polymorphisms may attenuate the protective effects of aspirin in breast cancer	51
PPAR-β/δ	rs2076167	Gastric	Asian, China	Case-control	196	397 (PB)	Self-reporting on dietary habits and smoking history Diagnosis with *H. pylori* infection	Increased risk among GG variant carrier with high dietary salt intake (5.11; 1.11–23.5 No interaction: risk did not vary among smoking and *H. pylori* positive subgroups No Interaction	The PPAR-β/δ rs2076167 G/G variant may enhance the mutagenic effect of salt in promoting cancer	93
	rs3734254 rs2016520 (5′-UTR-T/C)	Lung	Caucasian, USA	Case-control	1,553	1,730 (HB)	Self-reporting on tobacco smoking: Heavy, light, and nonsmoker	No interaction	PPAR-β/δ polymorphism does not modify the association between smoking and lung cancer risk	97
	rs3734254	Lung Upper aerodigestive tract (UADT)	Mixed, USA	Cross-sectional	611 601	–	Self-reporting on smoking and alcohol consumption:	CC variant was associated with survival in lung and UADT cancer	The PPAR-β/δ polymorphism decreases the risk of death among smokers with	95

(*continued*)

Table 3. Continued.

Gene	SNP	Cancer type	Ethnic group, country of study	Study design	#Participants		Environmental stimulus	GxE Interactions (OR;CI)	Comments	Study
					Cases	Controls (origin)[a]				
							Tobacco smokers were defined as those who had more than 100 cigarettes in their lifetime (in pack-years). Alcohol drinkers were defined as those who drank at least one alcoholic drink/month for at least 6 months (average number of drinks/day)	smokers. Inverse association of the rs3734254 CC variant with cancer mortality in smoker patients (0.55; 0.35–0.87); Weaker among nonsmoker patients (0.84; 0.31–2.28)	Lung and UADT cancer vs. non-smoker patients	
PPAR-γ	Pro12Ala	Bladder	Indians, Pakistan	Case-control	200	200 (PB)	Smoking status from medical records	No interaction	Pro12Ala polymorphism does not modify the association between smoking and urinary bladder cancer and prostate cancer risk	114
	Pro12Ala	Breast	Hispanic, Mexico	Case-control	197	220 (PB)	Measured urinary arsenic and arsenates levels	No interaction	Both Pro12Ala and Ala203Pro did not modify the association between the arsenic and breast cancer	69
	Pro12Ala	Breast	Hispanic, Mexico	Case-control	208	220 (PB)	Urinary phthalate metabolites levels	The association between MEHHP and breast cancer	Pro12Ala polymorphism increases breast cancer risk among	71

						using a first-void urine sampleb	risk was positively modified in carriers of polymorphism (1.80; 1.23–2.64)	subjects with higher MEHHP urinary levels compared to non-carriers	
Pro12Ala	Breast	Caucasian, Denmark	Nested case-control	361	361	Self-reporting on NSAIDs usage and alcohol drinking: NSAIDs use measured as 'any NSAID' with more than 2 pills per month during 1 year Alcohol consumption measured as average frequency of intake of six types of alcoholic beverage	Carriers of PPARγ2 Pro12Ala variant not using NSAID had a lower breast cancer risk (0.44; 0.26–0.73) vs. non-user carriers Non-carriers of PPARγ2 Pro12Ala variant consuming more than 10 g/day of alcohol had a higher breast cancer risk 1.21; 1.06–1.35)	Pro12Ala polymorphism protects from breast cancer in NSAID users Pro12Ala does not modify the association between alcohol consumption and breast cancer risk	75
PPARγ2 Pro12Ala PPARg3 C-681G	CRC	Asian, Singapore	Nested case-control	362	1,164 (PB)	Self-reporting on diet, smoking, and alcohol drinking: A smoker defined as a subject who ever smoked at least one cigarette/day for a year or longer An alcohol drinker defined as a subject who drank any alcoholic beverages on a	No Interaction; the associations between the combined genotypes of PPARγ2 and PPARγ3 and CRC risk were comparable among exposure subgroups	PPAR-γ Polymorphisms examined do not modify the association between alcohol/smoking and CRC risk	78

(*continued*)

Table 3. Continued.

Gene	SNP	Cancer type	Ethnic group, country of study	Study design	#Participants		Environmental stimulus	GxE Interactions (OR;CI)	Comments	Study
					Cases	Controls (origin)[a]				
							monthly basis or more often			
	Pro12Ala (rs1801282)	Gastric	Turkish, Turkey	Case-control	50	120 (HB)	Self-reporting on smoking and alcohol drinking	No Interaction	Pro12Ala does not modify the association between alcohol/smoking and gastric cancer	91
	Pro12Ala (C to G) rs3856806 (C to T)	Liver (HCC)	Asian, China	Case-control	584	923 (HB)	Self-reporting smoking, alcohol use, and diagnosis with hepatitis HBV infection	Decreased risk among non-smokers (0.32; 0.15–0.66) and non-alcohol users (0.40; 0.21–0.76) carrying GC, and among non-smokers (0.39; 0.20–0.77), and nonalcoholic users (0.47;0.26–0.86) carrying GC/GG High risk in non-smokers (2.24; 1.09–4.60) and nonalcoholic variant carriers (2.10; 1.05–4.19); *however interaction is not statistically significant among ever smokers and drinkers*	Pro12Ala is protective against HCC in males above 53 years that are never-smokers and never drinkers having a non-chronic HBV-infection rs3856806 polymorphism effect is modulated when carriers are exposed to alcohol and tobacco	121

rs1899951 (G to A)	Lung	Asian, China	Matched case-control	500	517 (PB)	Self-reporting on tobacco smoking: Smokers are defined as those who had smoked more than one cigarette/day (subgrouped as nonsmokers, light, and heavy smokers)	Higher risk among heavy smoker variant carriers (3.45; 1.43–8.58) compared to wild-type GG carriers	The rs1899951 intronic variant increases the risk of lung cancer in heavy smokers	96
Pro12Ala rs1801282	Lung	Caucasian, USA	Case-control	1,553	1,730 (HB)	Self-reporting on tobacco smoking: heavy, light, and nonsmoker	No interaction	Pro12Ala polymorphism does not modify the association between smoking and lung cancer risk	97
rs10865710 rs1801282 (Pro12Ala) rs3856806 rs13306747	Lung Upper aerodigestive tract (UADT)	Mixed, USA	Cross-sectional	611 601	–	Self-reporting on smoking and alcohol consumption	No interaction	PPAR-γ polymorphism did not modify the risk of death among smokers and drinkers with Lung and UADT cancers vs. nonsmoker and nondrinker patients	95
Pro12Ala	Prostate	Caucasian, Denmark	Nested case-control	370	370 (PB)	Self-reported NSAIDs usage defined as the weekly use of aspirin or an NA-NSAID	No interaction	Pro12Ala polymorphism does not modify the association between NSAID usage and prostate cancer risk	90
Pro12Ala	Prostate	Caucasian USA	Case-control	91	237 (PB)	BMI	Higher risk among Men with BMI $>$ 27.2 kg/m^2 carriers of the Pro12Ala variant compared to wild-type carriers (2.77; 1.25-6.16)	Overweight men that are carriers of the Pro12Ala polymorphism are more susceptible to prostate cancer	61

[a]Origin of controls if specified by source: population-based (PB); hospital-based (HB).
[b]Phthalates metabolites: mono-ethyl phthalate (MEP), mono-n-butyl phthalate (MBP), mono-iso-butyl phthalate (MiBP), MBzP, MCPP; DEHP metabolites: mono-(2-ethylhexyl) phthalate (MEHP), mono-(2-ethyl-5-hydroxyhexyl) phthalate (MEHHP), mono-(2-ethyl-5-oxohexyl) phthalate (MEOHP), and mono-(2-ethyl-5-carboxypentyl) phthalate (MECPP).

On the other hand, several PPAR-α genetic variants were found to modify the protective effects of aspirin in breast cancer.[51]

Previous studies have suggested that PPAR-γ may be playing a protective role in many malignancies and that PPAR-γ interaction with ligands would have an antitumor effect through decreasing cell growth and promoting apoptosis.[103] Similar roles for PPAR-β/δ in tumor suppressing and anti-apoptotic pathways were suggested, including regulation of growth promoting genes, such as c-Myc and Cyclin-D1.[104] Therefore, it is possible to postulate that certain functional mutations in the PPAR gene may be disrupting protective mechanisms, hence indirectly promoting tumorigenesis in cases of carcinogenic exposures, and directly triggering a wide range of metabolic alterations.[9] More studies are needed to examine the mechanistic nature of these PPAR-xenobiotic interactions and how they vary in their contribution to cancer risk for carriers of the different genetic variants.

In this review we identified a number of gaps in the literature. First, exposure assessment to carcinogenic substances was sparse. None of the reviewed studies assessed interaction of PPARs' polymorphism with polycyclic aromatic hydrocarbons (PAHs), heterocyclic amines (HCAs), diesel exhaust (DE), or other known potent carcinogens that are implicated in different types of cancer, including lung, bladder, and gastrointestinal tumors.[105] HCAs and PAHs, in particular, are ubiquitous environmental carcinogens that may arise from various sources including air pollution, tobacco smoking, and consumption of processed and/or overcooked meat. Examining their PPAR interactions is imperative considering *in vitro* and *in vivo* evidence on their strong ability to activate PPAR-α and PPAR-β/δ.[106] Similarly, reports on diesel showed that DE-nanoparticles include components capable of acting as PPAR-α antagonists.[107] Therefore, these common exposures may be modulating cancer risk in relation to the different PPAR polymorphisms, and hence should be examined and assessed accurately in future studies. Moreover, in the assessed exposures examined in this review, particularly in studies that relied on interview-based questionnaires, a major limitation was the dose assessment. For instance, Vogel et al. 2007 argues that the discrepancy in their results compared to those of Memisoglu et al. 2002 is mainly due to the fact that they actually estimated the amount of alcohol consumption among Danish women, otherwise, the PPAR-γ Pro12Ala variant would not have shown an interaction in its association with increased breast cancer risk.[74,75] Second, none of the PPARs were examined for GxE in either colon or prostate cancer, although in one study, a higher rectal cancer risk was found among the PPAR-γ Pro12Ala phenotype carriers that have a "high mutagen index" – computed based on the level of doneness, cooking method, and consumption of meat, poultry, and fish.[84] In addition, only one study examined the association between

PPAR-γ polymorphism and each of melanoma, thyroid, and bladder cancer. In the latter, Pro12Ala variant was found to be protective against bladder cancer in untreated patients, and to increase bladder cancer progression and recurrence in immunotherapy-treated patients.[101] Interestingly, a recent study described how a mutation in the RXRA protein triggers a PPAR-γ/PPAR-δ mediated proliferation of bladder cancer cells *in vitro*, and how this effect is reversed using PPAR antagonists.[108] Another recent *in vitro* study revealed an oncogenic role for PPAR-γ following a novel axis in the development of luminal bladder cancer.[109] Knowing the overwhelming evidence on the environmental etiology of bladder cancer, these recent findings call for further studies on the role of PPAR-γ in bladder cancer, aiming at defining the components of the PPAR-γ oncogenic-axis, and characterizing their interaction with putative carcinogens.

8. Conclusions

In summary, the current report highlights the role of PPARs in cancer risk and examined reported interactions between receptors' genetic polymorphisms and environmental exposures. Reviewed evidence points toward a possible gene–environment interaction, with more weight of evidence for PPAR-γ in breast cancer that deserves further mechanistic investigation. Evidence in other types of cancer remains controversial. In addition, there is a clear paucity of data on GxE interactions, while major data gaps remain in various types of cancer, particularly in colorectal, prostate, and bladder cancers. Progress in this area requires a comprehensive assessment of quantitative and reliable environmental exposure information using novel internal biomarkers of exposure, clearly a major deficiency in genetic-association studies. Despite current uncertainties, gaps, and limitations, the concept of PPAR–environment interactions modulating cancer risk seems to be a promising field. Understanding such interactions could in the future, fully delineate the potential for individually targeted approaches in cancer prevention and therapy.

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