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**QUEEN'S  
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## Investigation of shared genetic risk factors between Parkinson's disease and cancers

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# Investigation of Shared Genetic Risk Factors Between Parkinson's Disease and Cancers

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Additional Courage-PD (Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease), International Lung Cancer Consortium (ILCCO), and MMAC investigators are listed in the Appendix.

Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article, and they do not necessarily represent the decisions, policy, or views of the International Agency for Research on Cancer/World Health Organization.

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**ABSTRACT: Background:** Epidemiological studies that examined the association between Parkinson's disease (PD) and cancers led to inconsistent results, but they face a number of methodological difficulties.

**Objective:** We used results from genome-wide association studies (GWASs) to study the genetic correlation between PD and different cancers to identify common genetic risk factors.

**Methods:** We used individual data for participants of European ancestry from the Courage-PD (Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease; PD, N = 16,519) and EPITHYR (differentiated thyroid cancer, N = 3527) consortia and summary statistics of GWASs from iPDGC (International Parkinson Disease Genomics Consortium; PD, N = 482,730), Melanoma Meta-Analysis Consortium (MMAC), Breast Cancer Association Consortium (breast cancer), the Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (prostate cancer), International Lung Cancer Consortium (lung cancer), and Ovarian Cancer Association Consortium (ovarian cancer) (N comprised between 36,017 and 228,951 for cancer GWASs). We estimated the genetic correlation between PD and cancers using linkage disequilibrium score regression. We studied the association between PD and polymorphisms associated with cancers, and vice versa,

using cross-phenotypes polygenic risk score (PRS) analyses.

**Results:** We confirmed a previously reported positive genetic correlation of PD with melanoma ( $G_{\text{corr}} = 0.16$  [0.04; 0.28]) and reported an additional significant positive correlation of PD with prostate cancer ( $G_{\text{corr}} = 0.11$  [0.03; 0.19]). There was a significant inverse association between the PRS for ovarian cancer and PD (odds ratio [OR] = 0.89 [0.84; 0.94]). Conversely, the PRS of PD was positively associated with breast cancer (OR = 1.08 [1.06; 1.10]) and inversely associated with ovarian cancer (OR = 0.95 [0.91; 0.99]). The association between PD and ovarian cancer was mostly driven by rs183211 located in an intron of the *NSF* gene (17q21.31).

**Conclusions:** We show evidence in favor of a contribution of pleiotropic genes to the association between PD and specific cancers. © 2023 The Authors. *Movement Disorders* published by Wiley Periodicals LLC on behalf of International Parkinson and Movement Disorder Society. This article has been contributed to by U.S. Government employees and their work is in the public domain in the USA.

**Key Words:** Parkinson's disease; cancer; genetic correlation; polygenic risk score; pleiotropy

## Introduction

Although the frequency of cancers and neurodegenerative diseases increases with age, their cellular consequences are very different, with cell proliferation in cancers and neuronal death in neurodegenerative diseases. Parkinson's disease (PD) is caused by the loss

of dopaminergic neurons in the substantia nigra pars compacta.

Epidemiological studies that examined the association between PD and cancer support a general inverse association, ie, patients with PD tend to have a lower risk for cancer in general and cancer patients have a lower risk for PD.<sup>1</sup> This inverse association is mostly

explained by an inverse association with smoking-related cancers (lung, bladder, and colorectal cancers) because of a lower prevalence of smoking in patients with PD, but an inverse association has also been reported for some non-smoking-related cancers.<sup>1,2</sup> In addition, after stratification on smoking status, two studies found an inverse association between smoking-related cancers and PD among ever smokers, whereas there was a positive association among never smokers,<sup>3,4</sup> in favor of an interaction with smoking. In addition to smoking, other exposures associated with PD and cancer risk (eg, physical activity, reproductive factors in women) may also contribute to confound PD–cancer associations. Other possible biases in epidemiological studies include diagnostic bias, competing risks, or selective survival.<sup>5–7</sup>

Alternatively, positive associations between PD and specific cancers (melanoma, skin, breast, brain, and prostate) have also been reported.<sup>1,8</sup> In particular, the positive association between PD and melanoma is well established.<sup>9</sup> This association exists both for melanomas occurring before and after PD diagnosis, which does not support the role of antiparkinsonian medications as a causal factor.<sup>10</sup> It has been hypothesized that this association could be explained by common genetic factors, because people with a familial history of melanoma had an increased risk for PD and, conversely, relatives of patients with PD had an increased risk for melanoma.<sup>1</sup>

Specific genes involved in familial forms of PD (*SNCA*, *Parkin*, *LRRK2*) have been implicated in biological mechanisms associated with breast, prostate, and thyroid cancers.<sup>1,11,12</sup> Inactivation of *PARK2*, a gene that causes recessive forms of PD, is associated with an increased cancer risk, highlighting its role as tumor suppressor,<sup>13</sup> particularly in breast and ovarian cancers.<sup>14</sup> Epidemiological studies support an increased risk for cancer in *LRRK2*-G2019S carriers.<sup>15</sup> There is also an overrepresentation of somatic mutations of *PARK* genes in melanoma cases.<sup>16</sup> *PARK6* (*PINK1*) is also known to play a role in breast and ovarian cancers.<sup>17</sup>

A two-sample Mendelian randomization analysis did not find evidence in favor of a causal relationship between several cancers (including melanoma, breast, and prostate) and PD, thus suggesting that the previously reported associations between PD and cancers may be explained by pleiotropic genetic factors or shared biology.<sup>18</sup> A study using a candidate gene approach found no association between PD (Population Architecture through Genomics and Environment [PAGE] study, International Parkinson Disease Genomics Consortium [iPDGC]) and genetic polymorphisms associated with melanoma or skin pigmentation in genome-wide association studies (GWASs).<sup>19</sup> One study used iPDGC and 23andMe to show a positive significant genetic correlation between melanoma and PD.<sup>20</sup> Another study examined the genetic correlation between three neurodegenerative diseases and multiple cancers; for PD, they also used iPDGC and 23andMe data and showed positive

correlations with melanoma and prostate cancers, although these associations would not have been statistically significant after correction for multiple testing.<sup>21</sup>

In this article, we aimed at identifying common genetic risk factors of PD and cancers previously associated with PD (melanoma, breast, prostate) or for which an association is suspected (lung, ovary, thyroid). First, we estimated genetic correlations between PD and cancers using results from large GWASs and linkage disequilibrium (LD) score regression. Second, we analyzed the association of polygenic risk scores (PRSs) for PD (and their individual single-nucleotide polymorphisms [SNPs]) with each cancer and, conversely, the association of PRSs for each cancer (and their individual SNPs) with PD.

## Subjects and Methods

### GWAS Datasets on PD

We used data from two PD consortia: individual data from the Courage-PD consortium (Comprehensive Unbiased Risk Factor Assessment for Genetics and Environment in Parkinson's Disease)<sup>22</sup> and summary statistics from iPDGC.<sup>23,24</sup>

In Courage-PD, we excluded studies performed in Asian populations, studies that included cases only, and those with less than 50 cases and 50 controls. Only individuals from European ancestry were retained for the analysis. We also excluded individuals overlapping with iPDGC. We finally used data from 23 of 35 case–control studies, totaling 8919 cases and 7600 controls (Table S1). The NeuroChip array was used to genotype all the samples (see Supporting Information Methods). Imputation of autosomal variants was performed separately in each study, based on 271,398 to 373,664 SNPs. The mean number of SNPs available in each study after imputation was 13,710,549. In each study, SNP frequencies were compared in cases versus controls under an additive model using logistic regression adjusted for sex and the first four principal components. We meta-analyzed the summary statistics from the 23 GWASs using an inverse-variance fixed-effects ( $I^2 \leq 25\%$ ) or random-effects ( $I^2 > 25\%$ ) model (see Supporting Information Methods).

As a replication dataset for PD, we used GWAS summary statistics from the iPDGC consortium (33,674 cases, 449,056 controls).<sup>23</sup> Sex-stratified summary statistics are also available for 13,020 male PD cases, 7936 paternal proxy cases, 89,660 male controls, 7947 female PD cases, 5473 maternal proxy cases, and 90,662 female controls.<sup>24</sup>

### GWAS Datasets on Cancer

We used summary statistics from European ancestry-based GWASs on cancer susceptibility: Breast Cancer Association Consortium (BCAC)<sup>25</sup> (122,977 breast



cancer cases, 105,974 controls), Melanoma Meta-Analysis Consortium (MMAC)<sup>26</sup> (12,814 melanoma cases, 23,203 controls), Prostate Cancer Association Group to Investigate Cancer Associated Alterations in the Genome (PRACTICAL)<sup>27</sup> (79,148 prostate cancer cases, 61,106 controls), International Lung Cancer Consortium (ILCCO)<sup>28</sup> (29,266 lung cancer cancers, 56,450 controls), Ovarian Cancer Association Consortium (OCAC)<sup>29</sup> (25,509 ovarian cancer cases, 40,941 controls), and Epidemiology of Thyroid Cancer Consortium (EPITHYR)<sup>30</sup> (1554 differentiated thyroid cancer cases, 1973 controls).

### LD Score Regression

To investigate the genetic correlation between PD and each cancer, we performed cross-trait LD score regression.<sup>31</sup> We performed one analysis for each PD–cancer pair using summary statistics from the corresponding GWAS. Before running the analyses, we implemented the following filters<sup>31</sup>: SNPs with imputation scores INFO > 0.9; minor allele frequency (MAF) > 0.01; harmonized to HapMap3 SNPs with 1000 Genomes EUR MAF > 0.05; and removal of indels, structural variants, strand-ambiguous SNPs, and SNPs whose alleles did not match those in 1000 Genomes. This was performed by running the *munge-sumstats.pr* script included in *ldsc*. We ran *ldsc.py* from the *ldsc* package after excluding the *HLA* region. The final numbers of SNPs considered for each pairwise genetic correlation analysis are reported in Table S2.

Genetic correlations were estimated separately for Courage-PD and iPDGC and were then meta-analyzed using an inverse-variance weighting method. We used the false discovery rate (FDR) to take into account multiple testing.

### Cross-Phenotype PRS Analysis

Cross-phenotype PRS analysis allows investigating whether an individual-level genome-wide genetic prediction of a disease has substantive power to predict another disease. For each PD–cancer pair, we examined the association of the PRS for one of the diseases with the other disease, and vice versa.

PRSs for each cancer were aligned in Courage-PD using independent genome-wide significant SNPs and corresponding weights for PRS previously published in the largest GWAS to date on this cancer.<sup>27,28,32–36</sup> The lists of SNPs and corresponding weights used for cancer PRSs are described in Table S3A–F. The association between cancer PRSs and PD was examined in each of the 23 studies of Courage-PD using logistic regression adjusted for sex and four principal components. An inverse-variance weighted meta-analysis of regression coefficients was then performed. The extent of heterogeneity was estimated using the  $I^2$  statistic.<sup>37</sup> A random-effects meta-analysis was performed if  $I^2 > 25\%$ , and a

fixed-effects model was used otherwise. The association between cancer PRSs and PD was calculated in iPDGC, for which individual data were not available, using the *grs.summary* function from the *gtx* R package<sup>38</sup> based on summary statistics.

Analyses of the PD PRS in cancer were based on both 88 SNPs identified by Nalls et al<sup>23</sup> and 44 SNPs identified by Chang et al<sup>39</sup> to compare the results. For non-retrieved SNPs, we searched for proxies at  $r^2 > 0.8$  with the *proxysnps* function based on the 1000 Genomes Project (<https://github.com/slowkow/proxysnps>). We did not use one palindromic SNP (rs1555399) with MAF > 0.45. For thyroid cancer, we used the same strategy as for cancer PRSs in Courage-PD because individual data were available. For all other cancers for which individual data were not available, we used the same strategy as for the analysis between cancer PRSs and PD using summary statistics from iPDGC. Results of associations with PRSs for cancers in Courage-PD and iPDGC were meta-analyzed using the inverse-variance weighting method as described earlier. We calculated an FDR to correct for multiple testing for each direction of the cross-phenotype PRS analysis.

### Shared Risk Loci

For PD–cancer pairs for which we identified a significant cross-phenotype PRS association, we further explored associations at the level of individual SNPs from the PRSs, to identify pleiotropic risk loci that influence these associations. For each PD–cancer pair, we determined which SNPs played a role while correcting for multiple testing using the FDR.

### Stratified Analyses

Information on sex was available in Courage-PD and the latest iPDGC GWAS.<sup>24</sup> We examined the association of cancer PRSs with PD in men and women to identify sex-specific associations.

In addition, the ILCCO consortium performed GWASs stratified by smoking status (ever/never) and histology (small cell carcinoma, squamous cell carcinoma, and adenocarcinoma). This allowed us to examine the association of PD PRSs with lung cancer risk according to histology and smoking status.

## Results

### LD Score Regression

The meta-analysis of genetic correlations identified two significant positive genetic correlations of PD with melanoma ( $G_{\text{corr-meta}} = 0.16$ ,  $P_{\text{meta}} = 0.02$ , FDR = 0.047) and prostate cancer ( $G_{\text{corr-meta}} = 0.11$ ,  $P_{\text{meta}} = 0.01$ , FDR = 0.047) that remained significant after correction for multiple testing (FDR < 0.05) (Table 1). There was no heterogeneity between the Courage-PD

**TABLE 1** Genetic correlations between PD and cancers

Cancer	Courage-PD			iPDGC			Meta-analysis				
	G <sub>corr</sub>	CI <sub>95%</sub>	P	G <sub>corr</sub>	CI <sub>95%</sub>	P	G <sub>corr</sub>	CI <sub>95%</sub>	P <sub>meta</sub>	P <sub>het</sub>	FDR
Breast cancer	0.06	[-0.06; 0.18]	0.36	0.04	[-0.06; 0.14]	0.46	0.05	[-0.03; 0.13]	0.24	0.84	0.37
Ovarian cancer	0.04	[-0.20; 0.28]	0.74	-0.13	[-0.27; 0.01]	0.07	-0.09	[-0.21; 0.03]	0.17	0.23	0.33
Melanoma	0.18	[-0.02; 0.38]	0.09	0.14	[-0.02; 0.30]	0.08	0.16	[0.04; 0.28]	0.02	0.80	0.047
Thyroid cancer	0.28	[-0.05; 0.61]	0.10	-0.02	[-0.33; 0.29]	0.88	0.11	[-0.13; 0.35]	0.32	0.19	0.39
Prostate cancer	0.11	[-0.03; 0.25]	0.10	0.11	[-0.01; 0.23]	0.05	0.11	[0.03; 0.19]	0.01	0.98	0.047
Lung cancer	0.14	[-0.02; 0.30]	0.10	-0.05	[-0.02; 0.09]	0.40	0.02	[-0.08; 0.12]	0.72	0.07	0.72

Abbreviations: PD, Parkinson's disease; iPDGC, International Parkinson Disease Genomics Consortium; CI<sub>95%</sub>, 95% confidence interval; G<sub>corr</sub>, genetic correlation; P<sub>meta</sub>, P value from the meta-analysis of both datasets; FDR, false discovery rate.

**TABLE 2** Association between cancer PRSs and PD

PRS	Courage-PD		iPDGC		Meta-analysis			
	OR [CI <sub>95%</sub> ]	P	OR [CI <sub>95%</sub> ]	P	OR [CI <sub>95%</sub> ]	P <sub>meta</sub>	P <sub>het</sub>	FDR
Breast cancer	1.05 [0.98; 1.12]	0.17	1.04 [0.99; 1.10]	0.15	1.04 [1.00; 1.09]	0.05	0.86	0.10
Ovarian cancer	0.88 [0.80; 0.96]	$5.2 \times 10^{-3}$	0.90 [0.84; 0.96]	$1.2 \times 10^{-3}$	0.89 [0.84; 0.94]	$2.1 \times 10^{-5}$	0.76	$1.1 \times 10^{-4}$
Melanoma	0.99 [0.86; 1.15]	0.90	1.09 [0.98; 1.22]	0.11	1.06 [0.97; 1.15]	0.22	0.29	0.33
Thyroid cancer	1.02 [0.96; 1.08]	0.53	1.00 [0.96; 1.05]	0.96	1.01 [0.97; 1.04]	0.65	0.66	0.65
Prostate cancer	1.01 [0.96; 1.07]	0.61	1.01 [0.97; 1.06]	0.57	1.01 [0.98; 1.05]	0.44	0.96	0.53
Lung cancer	1.00 [0.92; 1.09]	0.94	1.10 [1.03; 1.17]	$5.5 \times 10^{-3}$	1.06 [1.01; 1.12]	0.02	0.11	0.07

Abbreviations: PRS, polygenic risk score; PD, Parkinson's disease; iPDGC, International Parkinson Disease Genomics Consortium; OR, odds ratio; CI<sub>95%</sub>, 95% confidence interval; P<sub>meta</sub>, P value from the meta-analysis of both datasets; P<sub>het</sub>, P value of heterogeneity; FDR, false discovery rate.

and iPDGC datasets. The genetic correlation between PD and breast cancer was positive and consistent in both datasets, but not statistically significant ( $P_{\text{meta}} = 0.24$ , FDR = 0.37). The other three cancers showed heterogeneous genetic correlations in sizes and directions between Courage-PD and iPDGC.

### Cross-Phenotype PRS Analysis

Analyses of the association between cancer PRSs and PD are shown in Table 2. We found one significant inverse association between the PRS for ovarian cancer and PD ( $P_{\text{meta}} = 2.1 \times 10^{-5}$ , FDR =  $1.1 \times 10^{-4}$ ). Suggestive positive associations were observed for the PRS for breast cancer ( $P_{\text{meta}} = 0.05$ , FDR = 0.10) and lung cancer ( $P_{\text{meta}} = 0.02$ , FDR = 0.07) with PD, but these associations became nonsignificant after correction for multiple testing.

Regarding the association between the PD PRSs and cancers (Table 3), we found a positive association between both PD PRSs and breast cancer, with a stronger association for the PRS<sub>Chang</sub> (odds ratio [OR]

= 1.08,  $P = 4.6 \times 10^{-14}$ , FDR =  $2.7 \times 10^{-13}$ ) than PRS<sub>Nalls</sub> (OR = 1.03,  $P = 1.9 \times 10^{-4}$ , FDR =  $1.14 \times 10^{-3}$ ). We also found an inverse association between the PRS<sub>Chang</sub> and ovarian cancer (OR = 0.95,  $P = 0.013$ , FDR = 0.04); the association was similar for the PRS<sub>Nalls</sub>, but it was borderline significant and became nonsignificant after correction for multiple testing.

### Shared Risk Loci

We searched for pleiotropic SNPs between PD and breast cancer on one side, and between PD and ovarian cancer on the other side, by examining associations for individual SNPs included in the PD, breast cancer, or ovarian cancer PRSs (Tables S4A–D and S5A–D).

The PRSs for PD and ovarian cancer share a common region on locus 17q21.31 that was also associated with breast cancer (Tables 4 and 5). This region is represented by four SNPs in high LD: rs183211, rs17649553, rs62053943 (pairwise  $r^2 > 0.7$ ,  $D' = 1$  in 1000 Genome CEU), and rs117615688 ( $r^2 < 0.14$ ,  $D' = 1$  with the three other SNPs). Associations with these SNPs were



**TABLE 3** Association between PD PRSs and cancers

Disease	PRS <sub>Chang</sub>			PRS <sub>Nalls</sub>		
	OR [CI <sub>95%</sub> ]	P	FDR	OR [CI <sub>95%</sub> ]	P	FDR
Breast cancer	1.08 [1.06; 1.10]	$4.6 \times 10^{-14}$	$2.7 \times 10^{-13}$	1.03 [1.01; 1.05]	$1.9 \times 10^{-4}$	$1.14 \times 10^{-3}$
Ovarian cancer	0.95 [0.91; 0.99]	0.013	0.04	0.97 [0.94; 1.00]	0.07	0.21
Melanoma	1.04 [0.98; 1.11]	0.19	0.38	1.05 [1.00; 1.10]	0.43	0.43
Thyroid cancer	0.92 [0.79; 1.07]	0.30	0.45	0.93 [0.82; 1.05]	0.25	0.375
Prostate cancer	1.00 [0.97; 1.02]	0.80	0.80	1.01 [0.99; 1.03]	0.41	0.43
Lung cancer	0.94 [0.79; 1.13]	0.51	0.61	0.98 [0.95; 1.00]	0.16	0.32

Abbreviations: PD, Parkinson's disease; PRS, polygenic risk score; OR, odds ratio; CI<sub>95%</sub>, 95% confidence interval; FDR, false discovery rate.

**TABLE 4** SNPs of PRSs for PD associated with breast or ovarian cancer

Locus	Gene	SNP	Position (kb)	EA	BA	Weight in PRSs for PD		Cancer			
						OR <sub>Chang</sub>	OR <sub>Nalls</sub>	Type	OR	CI <sub>95%</sub>	P
2q11.2	MAP4K4	rs11683001	102,396	A	T	–	1.07	Breast	1.03	[1.01, 1.04]	$1.6 \times 10^{-4}$
2q11.2	MAP4K4	rs34043159	102,413	C	T	1.07	–	Breast	1.02	[1.01, 1.04]	$2.8 \times 10^{-4}$
6p21.32	/	rs9275326	32,666	C	T	1.17	–	Breast	1.03	[1.01, 1.05]	$1.8 \times 10^{-3}$
16q12.1	CASC16	rs4784227	52,599	T	C	1.08	–	Breast	1.24	[1.22, 1.26]	$6.8 \times 10^{-201}$
	CASC16	rs3104783	52,636	A	C	–	1.07	Breast	1.10	[1.09, 1.11]	$1.6 \times 10^{-52}$
17q21.2	RETREG3	rs12951632	40,741	T	C	–	1.07	Breast	0.98	[0.96, 0.99]	$5.1 \times 10^{-4}$
17q21.31	CRHR1	rs62053943	43,744	C	T	–	1.31	Ovarian	0.89	[0.85, 0.92]	$5.0 \times 10^{-9}$
							–	1.31	Breast	1.06	[1.04, 1.08]
	CRHR1	rs117615688	43,798	G	A	–	1.26	Ovarian	0.91	[0.86, 0.96]	$7.0 \times 10^{-4}$
							–	1.26	Breast	1.04	[1.01, 1.07]
MAPT	rs17649553	43,994	C	T	1.28	–	Ovarian	0.89	[0.87, 0.92]	$1.2 \times 10^{-12}$	
						1.28	–	Breast	1.05	[1.03, 1.07]	$1.5 \times 10^{-10}$
17q23.2	BRIP1	rs61169879	59,917	T	C	–	1.09	Breast	1.03	[1.02, 1.05]	$3.9 \times 10^{-3}$

Abbreviations: SNP, single-nucleotide polymorphism; PRS, polygenic risk score; PD, Parkinson's disease; EA, effect allele; BA, baseline allele; OR, odds ratio; CI<sub>95%</sub>, 95% confidence interval.

in the same direction for PD and breast cancer, but in the inverse direction with ovarian cancer. These SNPs are located in introns of three different genes: *NSF* (*N*-ethylmaleimide-sensitive factor, vesicle fusing ATPase), *MAPT* (microtubule-associated protein tau), and *CRHR1* (Corticotropin-Releasing Hormone Receptor 1). These results are in favor of a common haplotype associated with the three diseases. The inverse cross-phenotype association between PD and ovarian cancer was mostly driven by this locus. No other SNPs of the PD PRS were significantly associated with ovarian cancer (or conversely) after correcting for multiple testing.

Of the SNPs from the PD PRSs, six were significantly associated with breast cancer and were located at five different loci (Table 4): 2q11.2 (in an intron of

*MAP4K4*, mitogen-activated protein kinase 4), 6p21.32, 16q12.1 (intronic region of *CASC16*, cancer susceptibility 16), 17q23.2 (in an intron of *BRIP1*, BRCA1 interacting protein C-terminal helix 1) with SNPs associated in the same direction, and 17q21.2 with SNPs inversely associated (in an intron of *RETREG3*, reticulophagy regulator family member 3).

Of the SNPs from the breast cancer PRS, rs3566861 located at 16q12.1 was in common with the PRS<sub>Chang</sub>. The two SNPs at locus 16q12.1 from the breast cancer PRS are in high LD ( $r^2 = 0.87$ ,  $D' = 0.97$ ) and were associated with PD in iPDGC (rs4784227: OR = 1.08,  $P = 9.4 \times 10^{-5}$ ; rs3566861: OR = 1.08,  $P = 1.5 \times 10^{-4}$ ) (Table 5).

**TABLE 5** SNPs of PRSs for breast or ovarian cancer associated with PD

Locus	Gene	SNP	Position (kb)	EA	BA	Cancer			Courage-PD			iPDGC		
						Type	OR PRS	OR	CI <sub>95%</sub>	P	OR	CI <sub>95%</sub>	P	OR
16q12.1	CASC16	rs35668161	52,538	A	C	Breast	1.12	1.09	[1.03, 1.15]	$3.6 \times 10^{-3}$	1.08	[1.04, 1.12]	$1.5 \times 10^{-4}$	
	CASC16	rs4784227	52,599	T	C	Breast	1.11	1.07	[1.01, 1.14]	0.02	1.08	[1.04, 1.12]	$9.4 \times 10^{-5}$	
17q21.31	NSF	rs183211	44,788	A	G	Ovarian	1.25	0.78	[0.74, 0.83]	$1.8 \times 10^{-17}$	0.81	[0.77, 0.84]	$9.0 \times 10^{-21}$	

Abbreviations: SNP, single-nucleotide polymorphism; PRS, polygenic risk score; PD, Parkinson's disease; iPDGC, International Parkinson Disease Genomics Consortium; EA, effect allele; BA, baseline allele; OR PRS, odds ratio of the PRS; OR, odds ratio; CI<sub>95%</sub>, 95% confidence interval.

## Stratified Analyses

Associations of the cancer PRSs with PD in men and women are shown in Table S6A,B. The inverse association between the ovarian cancer PRS and PD was present both in women ( $P_{\text{meta}} = 3.23 \times 10^{-4}$ ) and in men ( $P_{\text{meta}} = 1.38 \times 10^{-4}$ ) with the same effect size (OR = 0.88) and similar associations in Courage-PD and iPDGC. The association of the breast cancer PRS with PD was stronger in men (OR = 1.08,  $P_{\text{meta}} = 3 \times 10^{-3}$ ), in whom it was driven by iPDGC, than in women (OR = 1.05,  $P_{\text{meta}} = 0.07$ ). The association between the lung cancer PRS and PD was present only in women (OR = 1.08,  $P = 0.04$ ).

Associations between the PD PRS with different histology types of lung cancer are presented in Table S7. An inverse association was found between the PRS<sub>Nalls</sub> and squamous cell carcinoma (OR<sub>Nalls</sub> = 0.94,  $P_{\text{Nalls}} = 8.0 \times 10^{-3}$ ). The association with PRS<sub>Chang</sub> was in the same direction, but not significant (OR<sub>Chang</sub> = 0.98,  $P_{\text{Chang}} = 0.42$ ). Stratified analyses by smoking status in lung cancer showed an inverse association in ever smokers (OR<sub>Chang</sub> = 0.96,  $P_{\text{PRS-Chang}} = 0.086$ ; OR<sub>Nalls</sub> = 0.95,  $P_{\text{PRS-Nalls}} = 9.6 \times 10^{-3}$ ), but not in never smokers (OR<sub>Chang</sub> = 1.07,  $P_{\text{PRS-Chang}} = 0.28$ ; OR<sub>Nalls</sub> = 1.02,  $P_{\text{PRS-Nalls}} = 0.73$ ) (see Table S8). However, the interactions between the PD PRSs and smoking status did not reach statistical significance ( $P_{\text{PRS-Chang}} = 0.097$ ,  $P_{\text{PRS-Nalls}} = 0.20$ ).

## Discussion

In this article, we investigated whether pleiotropy plays a role in the association between PD and cancers using GWAS data from two PD and six cancer consortia. We found significant positive genetic correlations of PD with melanoma and prostate cancer. Cross-phenotype analyses showed that the PD PRS was associated with a higher risk for breast cancer and a lower risk for ovarian cancer. The ovarian cancer PRS was also associated with a lower risk for PD.

Our finding of a positive correlation of PD with melanoma and prostate cancer is consistent with epidemiological studies reporting positive associations of PD with melanoma,<sup>1,10</sup> whereas different directions of associations have been reported between PD and prostate cancer.<sup>1,40</sup> The genetic correlation we identified between PD and melanoma ( $G_{\text{corr}} = 0.16$  [0.04; 0.28]) is consistent with a previous study that used iPDGC and 23andMe data<sup>39</sup> to show a significant correlation of a similar magnitude ( $G_{\text{corr}} = 0.17$  [0.10; 0.24]).<sup>20</sup> Another study examined the genetic correlation between three neurodegenerative diseases and multiple cancers; analyses for PD were based on iPDGC and 23andMe data and showed a significant positive correlations with melanoma ( $G_{\text{corr}} = 0.14$ ,  $P = 0.044$ ) and

prostate cancer (iPDGC:  $G_{\text{corr}} = 0.09$ ,  $P = 0.032$ ; 23andMe:  $G_{\text{corr}} = 0.16$ ,  $P = 0.044$ ) that would not have survived multiple testing correction.<sup>21</sup> The authors also investigated the genetic correlation of PD with breast, ovarian, lung, and thyroid cancers and found no associations. The main difference between these two studies and ours is that, in addition to iPDGC data (excluding 23andMe), we also used data from a completely independent GWAS from the Courage-PD consortium.

We did not find significant correlations between PD and other cancers. However, the lack of correlation may be because of the fact that LD score allows to highlight only an overall trend of correlation. If shared loci of two diseases are randomly associated in different directions, an overall correlation would be masked by positively and negatively correlated regions that cancel each other out.

We explored the cross-phenotype PRS association between PD and cancers using two PRSs for PD. This allowed us to compare the results from the PRS proposed by Nalls et al<sup>23</sup> and the previous one proposed by Chang et al.<sup>39</sup> The PRS<sub>Nalls</sub> is more recent and included a higher number of SNPs but was determined in a population composed partly of proxy cases that could have led to some dilution of associations because of a less precise characterization of the disease. Both PD PRSs were associated with a higher risk for breast cancer. The breast cancer PRS was also associated with a higher risk for PD, but the association was no longer significant after correction for multiple testing. In addition, cross-phenotype analyses showed that the PD-PRS<sub>Chang</sub> was associated with a lower risk for ovarian cancer. Consistently, the ovarian cancer PRS was also associated with a lower risk for PD. Associations between both PD PRSs with each cancer were consistent, but the association with ovarian cancer reached significance only for the PRS<sub>Chang</sub>. To our knowledge, no published study has previously performed analyses of the cross-phenotype associations between PD and cancer.

Analyses of the associations between SNPs of the PRSs highlighted in cross-phenotype analyses showed that the inverse association between PD and ovarian cancer was mostly driven by one SNP in the 17q21.31 region. Three SNPs in this region were positively associated with breast cancer; they were not in LD with *BRCA1*, which is also located in this region. The gene *MAPT* in this region, tagged by SNPs of the PD-PRS, was already known as a potential predictive marker in epithelial ovarian cancer patients treated with paclitaxel/platinum first-line chemotherapy and as a marker of paclitaxel sensitivity in breast cancer.<sup>1</sup> Also, the gene *NSF* of the ovarian cancer PRS has already been reported to be associated with PD through the same SNP: rs183211. This gene has also been recently reported as associated with cancer pleiotropy (breast,

cervix, lung, melanoma, testis) in a pan-cancer study.<sup>41</sup> Four other regions from the PD PRS were associated with breast cancer in the same direction (2q11.2, 6p21.32, 16q12.1, 17q23.2) and one region in the opposite direction (17q21.2). The breast cancer PRS was not significantly associated with PD after correction for multiple testing, but the positive association was detected at a suggestive threshold. Sex-stratified analyses did not show major differences between men and women in the association of the PRS for both ovarian cancer and breast cancer with PD.

We detected another positive association between PD and the PRS for lung cancer that was significant in iPDGC, but not in Courage-PD; in sex-stratified analyses, this positive association was present in women only, whereas it tended to be inverse, although not significant, in men. We also found an inverse association between the PD PRS<sub>Nalls</sub> and squamous carcinomas of the lung. Cross-phenotype analyses of lung cancer stratified by smoking status showed an inverse association in ever smokers, whereas the association was positive in never smokers. These findings are consistent with the facts that squamous carcinomas are known to be the lung cancer histological type with the strongest association with tobacco,<sup>28,42</sup> and that smoking rates are lower in women. There was a trend toward a gene-environment interaction that was not statistically significant, possibly because of the small number of never smokers compared with the number of ever smokers and small effect sizes.

Cross-phenotype PRS analyses in other cancers did not show any association with PD. However, multiple pleiotropic SNPs with different directions of associations may lead to diluting an association with PRSs.

The main strength of our study is that we used the largest GWAS available at the present date for several cancers together with two independent large PD datasets to replicate our findings, while correcting for multiple testing. Our study also has limitations. The size of the GWAS datasets was different for different phenotypes, and for some of them, we did not have access to individual data but rather GWAS summary statistics. The panels of SNPs available in each GWAS were also different, which could affect the results, especially for genetic correlation analysis. Although the NeuroChip array has reduced coverage compared with some other arrays, the tagging variant backbone of about 306,670 SNPs has good genome-wide resolution and allows to perform genome-wide imputation; in addition, we retained for our analyses SNPs with good-quality imputation ( $r^2 \geq 0.8$ ). Our analyses are restricted to participants of European descent, and additional studies are needed in other populations. Finally, except for the lung cancer GWAS that performed analyses stratified by smoking, analyses stratified by environmental factors were not available for other cancer GWASs.

Epidemiological studies have identified a complex association between PD and cancers, but the underlying mechanisms remain poorly understood. In addition, epidemiological studies on the relation between neurodegenerative diseases and cancer face a number of methodological difficulties and possible biases, including confounding, diagnostic bias, competing risks, or selective survival.<sup>5-7</sup> Alternatively, as for Mendelian randomization, the genetic approach we used is not affected by confounding, reverse causation, or surveillance biases because genes are randomly assigned at birth and are not influenced by exposures. In addition, we used GWASs for PD and cancer studies that were independent and did not include overlapping participants; hence in the cancer GWAS, the diagnosis was independent of PD, and vice versa. Studies based on a genetic approach are complementary to epidemiological studies and may help understand whether genetic pleiotropy could account for some of the associations highlighted by epidemiological studies. Our results suggest the importance of shared genetic variants between PD and some cancers. These analyses may be followed by analyses of genome-wide pleiotropy at a SNP, gene, or pathway level to better understand the shared biologic mechanisms between PD and cancer. It would also be interesting to explore additional environmental factors that could interact with pleiotropic genes associated with both PD and cancer. Evidence of pleiotropy between PD and cancer will improve our understanding of the etiology of these diseases and will provide insights into their underlying biology. ■

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## Appendix

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### Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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## Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.

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