No evidence for a causal relationship between cancers and Parkinson’s disease

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Abstract

Background: Epidemiological data suggest that cancer patients have a reduced risk of subsequent Parkinson’s disease (PD) development, but the prevalence of PD in melanoma patients is often reported to be increased. Causal relationships between cancers and PD have not been fully explored.

Objectives: To study causal relationship between different cancers and PD.

Methods: We used GWAS summary statistics of 15 different types of cancers and two-sample Mendelian randomization to study the causal relationship with PD.

Results: There was no evidence to support a causal relationship between the studied cancers and PD. We also performed reverse analyses between PD and cancers with available full summary statistics (melanoma, breast, prostate, endometrial and keratinocyte cancers) and did not find evidence of causal relationship.

Conclusions: We found no evidence to support a causal relationship between cancer and PD and the previously reported associations could be a result of genetic pleiotropy, shared biology or biases.
**Introduction**

Parkinson’s disease (PD) is a complex disorder, influenced by numerous environmental and genetic factors. Observational studies have suggested associations between PD and different types of cancers (lung, skin, pancreatic cancers and others) [1-7], such that cancer patients have lower risk of subsequent PD development [8] and overall PD is associated with a reduced risk of subsequent cancer development [1, 2]. However, risk of PD is increased in melanoma patients [9] and the prevalence of melanoma and brain tumors may be increased in patients with PD [3-6]. In the absence of a causal effect, apparent associations may be explained by confounding factors (such as toxins that casually influence the risk of specific cancers and PD), shared genetic susceptibility or biological pathways, or ascertainment bias [10, 11].

In Mendelian randomization (MR), similar to randomized control trials, single-nucleotide polymorphism (SNPs) are used to randomly divide participants into two groups defined by genotype, assuming that genotype distribution is a random process during meiosis, and therefore it should not be affected by confounders. MR uses SNPs associated with an exposure of interest (such as cancer susceptibility) as proxies to determine the causal association between that exposure and an outcome [12]. Summary level data from genome wide associational studies (GWASs) are used to construct instrumental variables (IVs) from GWAS significant SNPs. In the current study, we performed bi-directional MR to examine whether certain types of cancers have causal relationships with PD and vice versa.

**Methods**

**Mendelian randomization**

For the construction of genetic instruments, we selected studies from the GWAS Catalog [13] using the R package MRInstruments [14, 15]. First, we searched for traits using keywords “cancer”,...
“carcinoma”, “glioma”, “lymphoma”, “leukemia”, “melanoma”. We then selected the most recent available GWAS for each cancer, with a minimum of 1000 cases and at least the same number of controls of European ancestry. Additionally, recent GWASs on melanoma [16] and combined analysis of keratinocyte cancers [17] were added as they were not available in the GWAS catalog. Fifteen studies were selected for this part of the analysis (Supplementary Table 1). UK biobank (UKB) participants were included in some of these studies (colorectal cancer, combined analysis of keratinocyte cancers, endometrial cancer, lung cancer, melanoma, uterine fibroids).

To perform MR in the reverse direction (the causal relationship between PD and different cancer types) we required full summary statistics which we obtained through GWAS Catalog or direct contact with authors. We were able to collect full summary statistics for melanoma [16], breast [18], prostate [19], endometrial [20] and keratinocyte cancers (basal cell and squamous cell carcinoma) [17].

We used GWAS summary statistics from the latest PD GWAS excluding 23andMe and UKB data, to avoid potential bias due to overlapping samples [21]. After the exclusions, a total of 15,056 PD patients and 12,637 controls were included in the summary statistics [21].

We constructed genetic instruments for cancer susceptibility and PD using SNPs with GWAS significant p-values (<5×10^{-8}) from each study. The extracted data included rs-numbers, log odds ratios, standard errors, p-values, alleles, and effect allele frequency. SNPs for each exposure were clumped using standard parameters (clumping window of 10,000 kb, r^2 cutoff 0.001) to discard variants in LD. Additionally, we calculated r^2, which reflects the proportion of variability explained by genetic variants and F-statistics to estimate the strength of IVs selected for exposures as previously described [22, 23]. We calculated estimated power to detect an equivalent effect size of OR 1.2 on PD risk utilizing an online Mendelian randomization power calculation (https://sb452.shinyapps.io/power/) [24].
MR methods implemented in the Two-sample MR R package [14, 15] were used and are described in detail elsewhere [25-27]. Firstly, we performed Steiger filtering to exclude SNPs that explain more variance in the outcome than in the exposure [15]. We then used the inverse variance weighted (IVW) method, in which we pooled estimates from individual Wald ratios for each SNP and meta-analyzed using random effects [25-27]. We applied MR Egger to detect net directional pleiotropy and provide a better estimate of the true causal effect allowing to detect possible violations of instrumental variable assumptions [27]. Additionally, we used weighted median (WM) which is a median of the weighted estimates and provides consistent effect even if 50% of IVs are invalid [28]. These sensitivity analyses were performed to explore heterogeneity and horizontal pleiotropy. Heterogeneity was tested using Cochran’s Q test in the IVW and MR-Egger methods [29]. For each method, we constructed funnel plots to detect pleiotropic outliers (Supplementary Figure 1-6). Additionally, we performed MR-PRESSO test to detect outlier SNPs which may be biasing estimates through horizontal pleiotropy, and then adjust for them [30].

Data availability:

All code used in the current study is available at https://github.com/gan-orlab/MR_Cancers-PD

Results

Mendelian randomization does not support a causal role for different cancers and PD

We selected 15 cancer GWAS studies for MR analysis (Table 1). The variance in the exposure variables explained by SNPs ranged from 0.016 to 0.059 (Table 2). All instruments had F-statistics of >10, which is the standard cut-off applied to indicate sufficient instrument strength (Table 2; Supplementary Table 1).

No causal effect of any cancer on PD was observed applying various MR methods (Table 1; Supplementary Table 1, Supplementary Figure 1-2).
To test for potential violations of MR assumptions, we performed sensitivity analyses. Significant heterogeneity was apparent for cutaneous squamous cell carcinoma (IVW, Q p-value=0.02) and combined analysis of keratinocyte cancers (MR Egger, Q p-value=0.012; IVW, Q p-value=0.012, Supplementary Table 2, Supplementary Figure 3).

Tests for pleiotropy were performed to detect SNPs affecting the outcome through alternative pathways. There was some evidence for net horizontal pleiotropy for brain tumors (p=0.011) and cutaneous squamous cell carcinoma (p=0.029, Supplementary Table 2) which may have resulted in bias to IVW estimates, but the slopes from Egger regression were imprecisely estimated. Using MR-PRESSO, we detected an outlier SNP for cutaneous squamous cell carcinoma (rs4710154). The distortion test did not suggest significant changes in the effect estimates after this outlier was removed (Supplementary Table 2). The sensitivity analyses revealed no clear evidence for bias in the IVW estimate due to invalid instruments with other cancers.

Additionally, we performed reverse MR with melanoma, keratinocyte, prostate, endometrial and breast cancers for which we had full summary statistics using PD-associated SNPs as exposure and cancer summary statistics as outcome and did not find any evidence for causal relationships (Supplementary Table 3; Supplementary Figure 4-6). We found evidence for directional pleiotropy between PD and breast cancer and keratinocyte cancers, and a borderline distortion test with MR-PRESSO for breast cancer (Supplementary Table 3). MR-PRESSO identified an outlier SNP for both PD and breast and prostate cancer (rs4630591). Additionally, the rs510306 SNP was found to be an outlier for prostate cancer. For keratinocyte cancers, three outlier SNPs were detected (rs4630591, rs6599388 and rs4889603).

**Discussion**

In the current study, we performed a comprehensive analysis to examine whether the reported associations between different cancers (Table 1) and PD may be causal. Our results provide no
evidence to support causal effects, and indicate that the observed associations may be due to other reasons including shared biology, confounders or biases. MR methods have limited availability and statistical power to differentiate horizontal and vertical pleiotropy, but high power to detect pleiotropy itself. Although MR can help reduce confounding and the possibility of reverse causality, a recent study demonstrated that MR is not immune to survival bias [31]. PD is an age-related disease and inverse observational study associations may occur spuriously if the exposure of interest (here cancer) causes premature mortality. This situation is known as ‘survivor bias’ and can occur in case-control settings, including in MR studies. On the other hand, early mortality from cancer could reduce cancer prevalence in PD [8]. The higher occurrence of brain cancers in PD might be related to closer medical attention (i.e., more frequent MRI in PD patients compared to the general population).

The most thoroughly studied genetic relationship between cancer and PD is for melanoma [32]. Previous MR studies did not demonstrate evidence of a causal relationship between PD and melanoma [22]. However, a recent, comprehensive analysis suggested a significant genetic correlation between melanoma and PD, with gene expression overlap [10], that could probably explain the increased frequency of melanoma in PD. One of the possible explanations for the link between cancers and PD is pleiotropy. In our study, we only examined causality using MR and did not estimate possible shared biology. To study possible shared biology, methods such as linkage disequilibrium score regression and transcriptome wide association study can be used to examine correlations between two traits occurring through shared genetic architecture. Unfortunately, we were only able to collect full summary statistics of mostly sex-specific cancers (prostate, breast, endometrial cancers), which cannot be used with the PD GWAS data since it is not sex-stratified. This approach should be used in future studies. We cannot rule out that pleiotropic effects within the IVs cancel out each other if they have effects in opposite direction. There are genes involved in pathogenesis of both PD and cancers. It was suggested that familial PD genes (PINK1, DJ1, LRRK2 etc.) may play a role in cancers [33-35].
variants were associated with PD [36] and overexpression of GPNMB have been demonstrated in PD as well as in various cancers including melanoma [37, 38].

In our analyses using MR-PRESSO, we identified a few outlier SNPs. For cutaneous squamous cell carcinoma and PD, the rs4710154 SNP, located near the FGFR1OP gene, was an outlier. This gene was previously implicated in skin cancer and in several inflammatory disorders including Crohn’s disease [39]. This SNP was not previously associated with PD. Another outlier SNP, rs4630591, near the KANSL1 gene (encoding for KAT8 Regulatory NSL Complex Subunit 1) was identified for PD and breast and prostate cancers. This gene has been previously reported as the first cancer predisposition fusion gene [40], and this SNP was associated with breast cancer in transcriptome wide association study [41]. The rs510306 SNP near the IGSF9B gene has not been previously implicated in prostate cancer. For PD and keratinocyte cancers, three outlier SNPs were detected (rs4630591, rs6599388 and rs4889603). The rs6599388 SNP is located in TMEM175 and rs4889603 is located in STX1B, both of which have not been previously associated with skin cancers.

Our study has several limitations. This is a European-based study, and these associations or lack thereof should be studied in other populations. We excluded UKB data to decrease the chance of overlapping samples between studies, which can result in bias. As a result, some of our MR analyses might have not enough power to detect the causal effect. Lack of availability of sex-specific PD GWAS data is the another limitation, which would be important for studying the causal effect of sex-specific cancers, or with cancers that have meaningful sex differences [42]. We performed bi-directional MR with PD and cancers with available full summary statistics (melanoma, breast, prostate, endometrial and keratinocyte cancers) and did not find evidence of a causal relationships. One more limitation is that MR relies on the quality of the GWAS used for the MR, and thus, limited by the GWAS quality.

Additionally, we could not consider in the current analysis important environmental exposures that would be of interest for stratified analyses (e.g. smoking in lung cancer; hormone levels in sex-
driven cancers). Thus, it is possible that we missed some causal effects due to gene-environment interaction or imperfect phenotype consideration.

To conclude, our results do not support a causal relationship between the tested cancers and PD, and suggest that the observed associations could be a result of genetic pleiotropy, shared biology or biases. Once larger datasets become available, as well as sex-specific PD datasets, additional MR studies should be performed on cancers and PD.
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U19 CA148065, and Cancer UK Grant C1287/A16563. All studies and funders are listed in O'Mara et al (2018). The breast cancer genome-wide association analyses were supported by the Government of Canada through Genome Canada and the Canadian Institutes of Health Research, the ‘Ministère de l’Économie, de la Science et de l’Innovation du Québec’ through Genome Québec and grant PSR-SIIRI-701, The National Institutes of Health (U19 CA148065, X01HG007492), Cancer Research UK (C1287/A10118, C1287/A16563, C1287/A10710) and The European Union (HEALTH-F2-2009-223175 and H2020 633784 and 634935). All studies and funders supported breast cancer GWAS are listed in Michailidou et al., (Nature, 2017). For acknowledgements for the melanoma meta-analysis see Landi et al (Nature genetics, 2020). We would like to thank The PRACTICAL consortium, CRUK, BPC3, CAPS, PEGASUS. The Prostate cancer genome-wide association analyses are supported by the Canadian Institutes of Health Research, European Commission’s Seventh Framework Programme grant agreement n° 223175 (HEALTH-F2-2009-223175), Cancer Research UK Grants C5047/A7357, C1287/A10118, C1287/A16563, C5047/A3354, C5047/A10692, C16913/A6135, and The National Institute of Health (NIH) Cancer Post-Cancer GWAS initiative grant: No. 1 U19 CA 148537-01 (the GAME-ON initiative). We would also like to thank the following for funding support: The Institute of Cancer Research and The Everyman Campaign, The Prostate Cancer Research Foundation, Prostate Research Campaign UK (now PCUK), The Orchid Cancer Appeal, Rosetrees Trust, The National Cancer Research Network UK, The National Cancer Research Institute (NCRI) UK. We are grateful for support of NIHR funding to the NIHR Biomedical Research Centre at The Institute of Cancer Research and The Royal Marsden NHS Foundation Trust. The Prostate Cancer Program of Cancer Council Victoria also acknowledge grant support from The National Health and Medical Research Council, Australia (126402, 209057, 251533, 396414, 450104, 504700, 504702, 504715, 623204, 940394, 614296,), VicHealth, Cancer Council Victoria, The Prostate Cancer Foundation of Australia, The Whitten Foundation, PricewaterhouseCoopers, and Tattersall’s. EAO, DMK, and EMK acknowledge the Intramural Program of the National Human Genome Research Institute for their
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Conflict of Interest:
ZGO has received consulting fees from Lysosomal Therapeutics Inc., Idorsia, Prevail Therapeutics, Denali, Ono Therapeutics, Neuron23, Handl Therapeutics, Deerfield and Inception Sciences (now Ventus). None of these companies were involved in any parts of preparing, drafting and publishing this study. AJN received grants from the Barts Charity, Parkinson’s UK and Aligning Science Across Parkinson’s; and honoraria from Britannia, BIAL, AbbVie, Global Kinetics Corporation, Profile, Biogen, and Roche. The rest of the authors have nothing to report.
References


Oddsson A, Zink F, Halldorsson G, Sveinbjornsson G, Kristjansson RP, Davidson OB, Salvardsdottir A,
Table 1. List of all cancer GWAS studies selected for Mendelian randomization analysis

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<tr>
<th>Trait</th>
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<th>Initial sample size</th>
<th>Replication sample size</th>
<th>Power</th>
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<td></td>
<td>Cases</td>
<td>Controls</td>
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<tr>
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<td>Cases</td>
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<td>11,518</td>
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<td>10,784</td>
<td>20,406</td>
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<td>Rafnar et al., 2018[52]</td>
<td>16,595</td>
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Table 2. MR analysis between exposure (cancers) and outcome (PD).

<table>
<thead>
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<th>Exposure</th>
<th>N, SNPs included</th>
<th>r²</th>
<th>F-statistic s</th>
<th>MR Egger</th>
<th>Inverse variance weighted</th>
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<td>se</td>
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<td>120.4</td>
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<td>0.102</td>
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</tr>
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<td>Oral cavity and pharyngeal cancer</td>
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<td>198.2</td>
<td>0.008</td>
<td>0.376</td>
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<tr>
<td>Pancreatic cancer</td>
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<td>0.037</td>
<td>68.9</td>
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<td>0.152</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>74</td>
<td>0.02</td>
<td>38.9</td>
<td>-0.091</td>
<td>0.060</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>8</td>
<td>0.028</td>
<td>148.02</td>
<td>-0.145</td>
<td>0.241</td>
</tr>
<tr>
<td>Uterine fibroids</td>
<td>18</td>
<td>0.024</td>
<td>732.5</td>
<td>0.164</td>
<td>0.185</td>
</tr>
</tbody>
</table>

PD, Parkinson’s disease; N, number; r², proportion of variance in exposure variable explained by SNPs; F, statistics ‘strength’ of the genetic instrumental variable; b, beta; se, standard error, pval, p-value.
<table>
<thead>
<tr>
<th>Exposure</th>
<th>N, SNPs</th>
<th>R2</th>
<th>F-statistics</th>
<th>MR Egger</th>
<th>Inverse variance weighted</th>
<th>Simple mode</th>
<th>Weighted mode</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>b</td>
<td>se</td>
<td>pval</td>
<td>b</td>
</tr>
<tr>
<td>Breast cancer</td>
<td>107</td>
<td>0.016</td>
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<td>0.06</td>
<td>0.25</td>
<td>0.03</td>
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<tr>
<td>Chronic lymphocytic leukemia</td>
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<td>106.11</td>
<td>0.05</td>
<td>0.64</td>
<td>0.94</td>
<td>0.10</td>
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<tr>
<td>Colorectal cancer</td>
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<td>0.02</td>
<td>53.8</td>
<td>0.00</td>
<td>0.27</td>
<td>0.99</td>
<td>0.04</td>
</tr>
<tr>
<td>Cutaneous squamous cell carcinoma</td>
<td>23</td>
<td>0.03</td>
<td>405.2</td>
<td>-0.10</td>
<td>0.08</td>
<td>0.22</td>
<td>0.05</td>
</tr>
<tr>
<td>Combined analysis of keratinocyte cancers</td>
<td>68</td>
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<td></td>
<td>0.023</td>
<td>216.6</td>
<td></td>
<td>0.02</td>
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<td>-0.01</td>
</tr>
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<td>0.00</td>
<td>0.12</td>
<td>1.00</td>
<td>0.05</td>
</tr>
<tr>
<td>Lymphoma</td>
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<td>0.047</td>
<td>236.2</td>
<td>0.33</td>
<td>0.29</td>
<td>0.34</td>
<td>-0.01</td>
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<tr>
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<td>0.05</td>
<td>0.51</td>
<td>0.00</td>
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<tr>
<td>Non-glioblastoma glioma/Glioma</td>
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<td>0.052</td>
<td>88.03</td>
<td>0.10</td>
<td>0.05</td>
<td>0.05</td>
<td>-0.02</td>
</tr>
<tr>
<td>Oral cavity and pharyngeal cancer</td>
<td>4</td>
<td>0.059</td>
<td>198.2</td>
<td>0.01</td>
<td>0.38</td>
<td>0.99</td>
<td>0.09</td>
</tr>
<tr>
<td>Pancreatic cancer</td>
<td>16</td>
<td>0.037</td>
<td>68.9</td>
<td>-0.22</td>
<td>0.15</td>
<td>0.17</td>
<td>0.00</td>
</tr>
<tr>
<td>Prostate cancer</td>
<td>74</td>
<td>0.02</td>
<td>38.9</td>
<td>-0.09</td>
<td>0.06</td>
<td>0.13</td>
<td>-0.02</td>
</tr>
<tr>
<td>Renal cell carcinoma</td>
<td>8</td>
<td>0.028</td>
<td>148.02</td>
<td>-0.15</td>
<td>0.24</td>
<td>0.57</td>
<td>-0.03</td>
</tr>
<tr>
<td>Uterine fibroids</td>
<td>18</td>
<td>0.024</td>
<td>732.5</td>
<td>0.16</td>
<td>0.19</td>
<td>0.39</td>
<td>-0.01</td>
</tr>
</tbody>
</table>

R2 - proportion of variance in exposure variable explained by SNPs; F-statistics 'strength' of the genetic instrument variable b- beta; se- standard error, pval - p-value
<table>
<thead>
<tr>
<th>Exposure</th>
<th>MR Egger</th>
<th>Inverse variance weighted</th>
<th>Test for directional horizontal pleiotropy</th>
<th>MR-PRESSO distortion test</th>
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</thead>
<tbody>
<tr>
<td>Breast cancer</td>
<td>Q</td>
<td>Q</td>
<td>Q</td>
<td>Q</td>
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<tr>
<td>Chronic lymphocytic leukemia</td>
<td>115.83</td>
<td>105</td>
<td>0.22</td>
<td>116.51</td>
</tr>
<tr>
<td>Colorectal cancer</td>
<td>8.09</td>
<td>5</td>
<td>0.15</td>
<td>8.10</td>
</tr>
<tr>
<td>Cutaneous squamous cell carcinoma</td>
<td>34.79</td>
<td>33</td>
<td>0.38</td>
<td>34.82</td>
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<tr>
<td>Combined analysis of keratinocyte cancers</td>
<td>29.94</td>
<td>21</td>
<td>0.09</td>
<td>37.73</td>
</tr>
<tr>
<td>Endometrial cancer</td>
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<td>11</td>
<td>0.91</td>
<td>5.64</td>
</tr>
<tr>
<td>Lung cancer</td>
<td>8.34</td>
<td>8</td>
<td>0.40</td>
<td>8.56</td>
</tr>
<tr>
<td>Lymphoma</td>
<td>3.23</td>
<td>3</td>
<td>0.36</td>
<td>4.79</td>
</tr>
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<td>Melanoma</td>
<td>54.34</td>
<td>43</td>
<td>0.12</td>
<td>55.13</td>
</tr>
<tr>
<td>Non-glioblastoma glioma/Glioma</td>
<td>9.37</td>
<td>17</td>
<td>0.93</td>
<td>17.57</td>
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<tr>
<td>Oral cavity and pharyngeal cancer</td>
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<td>Renal cell carcinoma</td>
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<td>6</td>
<td>0.18</td>
<td>9.35</td>
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<td>Uterine fibroids</td>
<td>22.90</td>
<td>16</td>
<td>0.12</td>
<td>24.46</td>
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</tbody>
</table>

Q- Cochran’s Q test, df- degrees of freedom, se- standard error, pval- p-value, NA for distortion test if non outliers were available
Supplementary Table 3. Reverse MR analysis between exposure (Parkinson's disease) and outcome (cancers)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N, SNPs</th>
<th>MR Egger b</th>
<th>se</th>
<th>pval</th>
<th>Weighted median b</th>
<th>se</th>
<th>pval</th>
<th>Inverse variance weighted b</th>
<th>se</th>
<th>pval</th>
<th>Simple mode b</th>
<th>se</th>
<th>pval</th>
<th>Weighted mode b</th>
<th>se</th>
<th>pval</th>
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<tbody>
<tr>
<td>Breast cancer</td>
<td>15</td>
<td>0.01</td>
<td>0.06</td>
<td>0.82</td>
<td>0.02</td>
<td>0.02</td>
<td>0.38</td>
<td>0.04</td>
<td>0.02</td>
<td>0.08</td>
<td>-0.02</td>
<td>0.03</td>
<td>0.59</td>
<td>0.00</td>
<td>0.02</td>
<td>0.86</td>
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<tr>
<td>Endometrial cancer</td>
<td>15</td>
<td>-0.03</td>
<td>0.10</td>
<td>0.78</td>
<td>-0.04</td>
<td>0.04</td>
<td>0.31</td>
<td>-0.02</td>
<td>0.04</td>
<td>0.54</td>
<td>0.04</td>
<td>0.08</td>
<td>0.66</td>
<td>-0.04</td>
<td>0.06</td>
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</tr>
<tr>
<td>Melanoma</td>
<td>14</td>
<td>0.00</td>
<td>0.06</td>
<td>0.99</td>
<td>-0.01</td>
<td>0.03</td>
<td>0.64</td>
<td>0.02</td>
<td>0.02</td>
<td>0.47</td>
<td>-0.01</td>
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<td>0.88</td>
<td>0.02</td>
<td>0.02</td>
<td>0.40</td>
<td>0.00</td>
<td>0.04</td>
<td>0.99</td>
<td>0.00</td>
<td>0.03</td>
<td>0.98</td>
</tr>
<tr>
<td>Keratinocyte cancers</td>
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<td>0.05</td>
<td>0.08</td>
<td>0.55</td>
<td>0.04</td>
<td>0.03</td>
<td>0.24</td>
<td>0.00</td>
<td>0.03</td>
<td>0.91</td>
<td>0.08</td>
<td>0.06</td>
<td>0.22</td>
<td>0.10</td>
<td>0.04</td>
<td>0.02</td>
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Heterogeneity tests

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<th>Q_df</th>
<th>Q_pval</th>
<th>Inverse variance weighted Q</th>
<th>Q_df</th>
<th>Q_pval</th>
<th>MR-Egger intercept</th>
<th>se</th>
<th>pval</th>
<th>MR-PRESSO global</th>
<th>se</th>
<th>pval</th>
<th>MR-PRESSO distortion test</th>
<th>pval</th>
<th>pval</th>
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<tr>
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<td>50.38</td>
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<tr>
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<td>21.81</td>
<td>14</td>
<td>0.08</td>
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<tr>
<td>Prostate cancer</td>
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<td>0.02</td>
<td>0.01</td>
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</tr>
<tr>
<td>Keratinocyte cancers</td>
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<td>0.00</td>
<td>39.35</td>
<td>14</td>
<td>0.00</td>
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<td>0.01</td>
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<td>&lt;0.001</td>
<td>0.60</td>
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</tr>
</tbody>
</table>

b- beta; se- standart error, pval - p-value
Supplementary Figure 1. Forest plots showing point estimates of the exposures of interest, Exposure of interest at the top of each forest plot...

Supplementary Figure 2. Plots showing point estimates of the exposures of interest; Exposure of interest at the top of each plot...

Supplementary Figure 3. Funnel plots evaluated the presence of possible heterogeneity across the estimates. Exposure of interest at the top of each plot...

Supplementary Figure 4. Reverse MR (PD as exposure; Cancers as outcome). Forest plots showing point estimates of the exposures of interest, Exposure of interest at the top of each forest plot...

Supplementary Figure 5. Reverse MR (PD as exposure; Cancers as outcome). Plots showing point estimates of the exposures of interest; Exposure of interest at the top of each plot...

Supplementary Figure 6. Reverse MR (PD as exposure; Cancers as outcome). Funnel plots evaluated the presence of possible heterogeneity across the estimates. Exposure of interest at the top of each plot...
**Supplementary Figure 1. Forest plots showing point estimates of the exposures of interest, Exposure of interest at the top of each forest plot.**

Black points represent log-odds ratio of each SNP on the risk of PD. Red points represent the log-odds ration when combining all SNPs together (Inverse variance weighted and MR Egger methods). Lines from points represent 95% confidence intervals.
Breast cancer as exposure
Chronic lymphocytic leukemia as exposure
Cutaneous squamous cell carcinoma as exposure
Combined analysis of keratinocyte cancers as exposure
Endometrial cancer as exposure
Lung cancer as exposure
Lymphoma as exposure

rs3781093
rs4439895
rs312998813
rs34972832
rs6928977

All - Egger
All - IVW

MR effect size for 'exposure' on 'outcome'
Melanoma as exposure

- rs7941496
- rs2369633
- rs7705526
- rs10931936
- rs3780269
- rs7837822
- rs1801536
- rs113469387
- rs12290699
- rs10739220
- rs7902587
- rs2695237
- rs13178866
- rs12020592
- rs17132860
- rs171024
- rs1805008
- rs4237963
- rs143190905
- rs12473635
- rs7966207
- rs1126809
- rs13263376
- rs1805007
- rs132941
- rs570318
- rs408825
- rs16891982
- rs6994183
- rs12913382
- rs3217986
- rs1800440
- rs4731207
- rs4420522
- rs3339759
- rs1056927
- rs6596655
- rs73069846
- rs10859996
- rs6908626
- rs76798800
- rs6914598
- rs3950296
- rs32578
- rs4354713
- rs5766565

All - Egger
All - IVW

MR effect size for 'exposure' on 'outcome'
Non-glioblastoma glioma/glioma as exposure
Oral cavity and pharyngeal cancer as exposure
Pancreatic cancer

MR effect size for 'exposure' on 'outcome'
Prostate cancer

| rs62106670 | rs17599629 | rs10793821 | rs11691517 | rs1218582 | rs1182 | rs2680708 | rs7141529 | rs4924487 | rs1270884 | rs2121875 | rs1004030 | rs1894292 | rs10845938 | rs56232506 | rs1881502 | rs605483 | rs7127900 | rs4245739 | rs4711748 | rs9364554 | rs2928679 | rs1859962 | rs10934853 | rs9287719 | rs12785905 | rs3850699 | rs11650494 | rs10993994 | rs2735839 | rs4430796 | rs9306895 | rs10486567 | rs8102476 | rs684232 | rs7931342 | rs7968403 | rs2427345 | rs12956892 | rs1465618 | rs7679673 | rs17021918 | rs1447295 | rs8008270 | rs2660753 | rs80130819 | rs1933488 | rs11135910 | rs20441558 | rs4962416 | rs10936632 | rs10460109 | rs902774 | rs3771570 | rs5759167 | rs11665669 | rs721048 | rs4713266 | rs58133635 | rs12621278 | rs8465657 | rs4976790 | rs2242652 | rs74702681 | rs1048169 | rs39984059 | rs11863709 | rs6062509 | rs11214775 | rs7241993 | rs17621345 | rs2273669 | rs1935581 | rs7295014 |

All - Egger

All - IVW

MR effect size for 'exposure' on 'outcome'
Renal cell carcinoma
Uterine fibroids

rs117245733
rs4335411
rs10069690
rs7907606
rs78378222
rs2202282
rs11031731
rs10929757
rs507139
rs10917151
rs12484951
rs16991615
rs479404
rs7030354
rs66998222
rs12638862
rs141379009
rs4684433

All - Egger
All - IVW

MR effect size for 'exposure' on 'outcome'
Supplementary Figure 2. PD without UKBB. Plots showing point estimates of the exposures of interest; Exposure of interest at the top of each plot.
A plot relating the effect sizes of the SNP-exposure association and the SNP-outcome associations with standard error bars. Lines correspond to causal estimates using each of the methods.
Breast cancer as exposure
Chronic lymphocytic leukemia as exposure
Colorectal cancer as exposure
Cutaneous squamous cell carcinoma as exposure
Combined analysis of keratinocyte cancers as exposure
Endometrial cancer as exposure
Lymphoma as exposure
Melanoma as exposure
Non-glioblastoma glioma/Glioma as exposure
Oral cavity and pharyngeal cancer as exposure
Pancreatic cancer as exposure
Prostate cancer as exposure
Renal cell carcinoma as exposure
Uterine fibroids as exposure
Supplementary Figure 3. PD without UKBB. Funnel plots evaluated the presence of possible heterogeneity across the estimates. Exposure of interest at the top of each plot. Each SNPs represented by dots. Inverse variance weighted and MR Egger method averaged causal effect of all SNPs.
Breast cancer as exposure

MR Method

- Inverse variance weighted
- MR Egger

![Scatter plot showing 1/SE\(_N\) against \(\beta_N\).]
Chronic lymphocytic leukemia as exposure
Colorectal cancer as exposure
Cutaneous squamous cell carcinoma as exposure
Combined analysis of keratinocyte cancers as exposure
Endometrial cancer as exposure
Lung cancer as exposure
Lymphoma as exposure
Melanoma as exposure
Non-glioblastoma glioma/Glioma as exposure
Oral cavity and pharyngeal cancer as exposure
Pancreatic cancer as exposure
Prostate cancer as exposure
Renal cell carcinoma as exposure
Uterine fibroids as exposure
Supplementary Figure 4. Reverse MR (PD as exposure; Cancers as outcome). Forest plots showing point estimates of the exposures of interest, Exposure of interest at the top of each forest plot.
Breast cancer as outcome
Endometrial cancer as outcome
Melanoma as outcome
Prostate as outcome

MR effect size for 'exposure' on 'outcome'
Keratinocytes cancers
Supplementary Figure 5. Reverse MR (PD as exposure; Cancers as outcome). Plots showing point estimates of the exposures of interest; Exposure of interest at the top of each plot
Breast cancer as outcome
Endometrial cancer as outcome
Melanoma as outcome
Prostate as outcome
Keratinocytes cancers
Supplementary Figure 6. Reverse MR (PD as exposure; Cancers as outcome). Funnel plots evaluated the presence of possible heterogeneity across the estimates. Exposure of interest at the top of each plot.
Breast cancer as outcome
Endometrial cancer as outcome
Melanoma as outcome
Prostate cancer as outcome