Obstructive sleep apnea syndrome and causal relationship with female breast cancer: a mendelian randomization study

Xiao-Ling Gao¹, Zhi-Mei Jia², Fang-Fang Zhao², Dong-Dong An², Bei Wang², Er-Jing Cheng¹, Yan Chen¹, Jian-Nan Gong¹, Dai Liu¹, Ya-Qiong Huang², Jiao-Jiao Yang², Shu-Juan Wang²

¹Department of Respiratory and Critical Care Medicine, The Second Hospital of Shanxi Medical University, Taiyuan 030001, P.R. China  
²The Second Department of Clinical Medicine, Shanxi Medical University, Taiyuan 030000, P.R. China

Correspondence to: Xiao-Ling Gao; email: xiaoling_gao@aliyun.com  
Keywords: mendelian randomization, breast cancer, obstructive sleep apnea syndrome, causal relation  
Received: October 15, 2019  Accepted: January 2, 2020  Published: February 29, 2020

Copyright: Gao et al. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY 3.0), which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited.

ABSTRACT

Although observational studies have reported a positive association between obstructive sleep apnea syndrome (OSAS) and breast cancer (BC) risk, causality remains inconclusive. We aim to explore whether OSAS is associated with etiology of BC by conducting a two-sample Mendelian randomization (MR) study in a Chinese population and Asian population from the Breast Cancer Association Consortium (BCAC). We found a detrimental causal effect of OSAS on BC risk in the primary analysis of our samples (IVW OR, 2.47 for BC risk per log-odds increment in OSAS risk, 95% CI = 1.86-3.27; P = 3.6×10⁻¹⁰). This was very similar to results of the direct observational case-control study between OSAS and BC risk (OR = 2.80; 95% CI = 2.24-3.50; P =1.4×10⁻¹⁵). Replication in the Asian population of the BCAC study also supported our results (IVW OR, 1.33 for BC risk per log-odds increment in OSAS risk, 95% CI = 1.13-1.56; P = 0.0006). Sensitivity analyses confirmed the robustness of our findings. We provide novel evidence that genetically determined higher risk of OSAS has a causal effect on higher risk of BC. Further studies focused on the mechanisms of the relationship between OSAS and breast carcinogenesis are needed.

INTRODUCTION

Breast cancer (BC) ranks as the most common cancer and the second most common cause of death from cancers in women worldwide [1–4]. According to the report of the Global Burden of Disease (GBD) Study 2017, the estimated annual deaths of BC was 611.6 thousand, and the all-age years of life lost (YLLs) was 16400.7 thousand globally [5]. Sleep-related mechanisms, which might initiate, exacerbate or modulate the phenotypic expression of multiple diseases, have been widely investigated for their relationships with BC [6–8]. However, less investigation has explored the potential detrimental effects of obstructive sleep apnea syndrome (OSAS), which has become a highly prevalent condition throughout the lifespan [9–16].

OSAS, a sleep-related breathing disorder characterized by recurrent cessations of breathing during sleep, could lead to intermittent hypoxia and sleep fragmentation [17]. Chronic and intermittent hypoxia have been shown to play an essential role in the progress of carcinogenesis and tumor progression [18–20]. Many observational studies have implicated the potential detrimental role of OSAS in multiple cancers, although the results were inconsistent [6, 21–24]. The causality of OSAS and BC still remains unknown due to the inherent limitations in observational studies of confounding and reverse causation.

Mendelian randomization (MR), using genetic variants as an instrument variable (IV) for the exposure to estimate causal effects of modifiable risk factors on disease outcomes, could overcome the limitations of the
observational studies [25]. It has successfully adopted in a wide spectrum of diseases, including cancers, cardiovascular diseases, diabetes, and so on [16, 26–34]. In current study, we aims to performed a two-sample MR analysis to examine the causal effect of OSAS and etiology of BC.

RESULTS

Baseline characteristics of the included samples

As shown in Table 1, two case-control studies were conducted. The first study aimed to replicate the GWAS findings of OSAS, which were mostly identified in European population. Then, we evaluated associations of the positive variants with BC risk in the second case-control study. The distribution of age, body mass index (BMI), and smoking status were comparable between the cases and controls, while BC cases have more family history of cancer, and OSAS (Table 1, P<0.001).

Replication of OSAS loci and their associations with BC risk in Chinese population

All 23 OSAS risk loci identified by GWASs mostly in European population were presented in Supplementary Table 1. Among them, 13 variants met the standard of minor allele frequency (MAF) ≥ 5% in Chinese Han population and pairwise r2 < 0.8. As shown in Table 2, 5 proxy SNPs, including rs10097555, rs11074782, rs10777373, rs11588454, and rs11897825, were identified to be significantly associated with OSAS risk in Chinese samples (P<0.05). All of these five variants were in agreement with HWE in controls (P > 0.05). As shown in Table 3, we found rs10097555, rs11074782, rs10777373, rs11588454, and rs11897825 were significantly associated with BC risk, after adjusted for age, smoking status, family history of cancer and BMI (P<0.05). Minor alleles of SNP rs11588454 and rs11897825 was associated with decreased risk of BC. One of these five variants were associated with increased risk of BC, while those of rs10097555, rs11074782, rs10777373 were associated with decreased risk of BC.

MR analyses

The F-statistic for the 5 instrument SNPs were all well above the threshold of F >10 typically recommended for MR analyses. Table 4 presents the summary statistics of the five genetic variants used as instrumental variables in both our sample and Asian population of the BCAC study. Associations of genetically determined risk of OSAS with BC risk using multiple MR methods are shown in Table 5. We found evidence of a detrimental causal effect of OSAS on BC risk in the primary analysis of our samples (IVW OR, 2.47 for BC risk per log-odds increment in OSAS risk, 95% CI = 1.86-3.27; P = 3.6x10^-10). This was very similar to results of the direct observational case-control study between OSAS and BC risk (OR = 2.80; 95% CI = 2.24-3.50; P =1.4x10^-19). When we replicated our findings in the Asian population of the BCAC study, we also found the detrimental causal effect (IVW OR, 1.33 for BC risk per log-odds increment in OSAS risk, 95% CI = 1.13-1.56; P = 0.0006). Sensitivity analyses by MBE, penalized IVW, robust IVW, simple median, and weighted median method confirmed the robustness of our findings. For the potential pleiotropy effect, we didn’t find any other associations by searching MR-Base, PhenoScanner database and the GWAS catalog. The intercept from MR-Egger regression didn’t differed from zero (P>0.05). Also, MR-PRESSO analyses revealed that no potential outliers were detected in both our sample and Asian population of the BCAC study.

DISCUSSION

In current study, we applied a two-sample MR approach to comprehensively evaluate the causal relationships of OSAS and etiology of BC in both Chinese samples and Asian population of the BCAC study. The primary MR analyses showed that genetic predisposition to higher risk of OSAS was associated with higher risk of BC. Meanwhile, sensitivity analyses validated the robustness of the primary results. We also didn’t detect any pleiotropy effect of the IV for OSAS using series of methods. To the best of our knowledge, this should be first study which aims to explore the causal relationships between OSAS and risk of BC.

Sleep-related disorders is a series of different medical disorders of the sleep patterns, including dyssomnias, parasomnias, circadian rhythm sleep disorders, and others [35, 36]. Among them, OSAS is the most frequent type of respiratory disturbance [37]. It was estimated that OSAS owned a mean prevalence rate of 22% (range, 9-37%) in men and 17% (range, 4-50%) in women globally [38]. According to the results of a meta-analysis in Asian countries, China and India present the highest prevalence of OSAS [39]. Previous retrospective and prospective observational studies revealed there was a possible association between OSAS and elevated cancer risk, although it was not determined that whether it was a causal relationship [22, 40–43]. Even some studies reported null association or reversed conclusion that cancers and its related therapies caused the occurrence of OSAS [44–46]. Against this background, the implement of MR in the causal inference was much more essential. Recently, a MR analysis evaluated the associations of self-reported chronotype (morning or evening preference), insomnia symptoms, sleep duration, with BC risk using the UK Biobank data [16]. They identified a protective effect of
Table 1. Characteristics of women included in the mendelian randomization study.

| Variables                        | OSAS Cases (n=900) | Controls (n=1078) | P value | BC Cases (n=1200) | Controls (n=1200) | P value |
|----------------------------------|--------------------|-------------------|---------|-------------------|-------------------|---------|
| Age                              |                    |                   |         |                   |                   |         |
| ≥50                              | 462 (51.3%)        | 564 (52.3%)       | 0.662   | 685 (57.1%)       | 641 (53.4%)       | 0.071   |
| <50                              | 438 (48.7%)        | 514 (47.7%)       | 0.532   | 515 (42.9%)       | 559 (36.6%)       | 0.648   |
| Body mass index (BMI)            | 23.97±3.21         | 23.88±3.17        | 0.532   | 23.96±3.20        | 23.90±3.24        | 0.071   |
| Family history of cancer         |                    |                   |         |                   |                   |         |
| Yes                              | 113 (12.6%)        | 108 (10.0%)       | 0.074   | 289 (24.1%)       | 122 (10.2%)       | <0.001  |
| No                               | 787 (87.4%)        | 970 (90.0%)       |         | 911 (75.9%)       | 1078 (89.8%)      |         |
| Smoking status                   |                    |                   |         |                   |                   |         |
| Smokers                          | 160 (17.8%)        | 162 (15.0%)       | 0.099   | 215 (17.9%)       | 184 (15.3%)       | 0.089   |
| Non-Smokers                      | 740 (82.2%)        | 916 (85.0%)       |         | 985 (82.1%)       | 1016 (84.7%)      |         |
| OSAS                             |                    |                   |         |                   |                   |         |
| Yes                              | -                  | -                 |         | 289 (24.1%)       | 122 (10.2%)       | <0.001  |
| No                               | -                  | -                 |         | 911 (75.9%)       | 1078 (89.8%)      |         |

Table 2. Replication of the GWAS identified OSAS variants in Chinese population.

|                  | OSAS cases | Controls | OR (95% CIs) * | P value |
|------------------|------------|----------|----------------|---------|
| rs10097555       |            |          |                |         |
| AA               | 621        | 691      | 1.00 (Reference)|         |
| AG               | 267        | 355      | 0.84 (0.69-1.01)| 0.069   |
| GG               | 12         | 32       | 0.42 (0.22-0.8)| 0.009   |
| G vs A           |            |          | 0.80 (0.71-0.90)| 0.001   |
| rs11074782       |            |          |                |         |
| CC               | 606        | 680      | 1.00 (Reference)|         |
| TC               | 267        | 343      | 0.87 (0.72-1.06)| 0.171   |
| TT               | 27         | 55       | 0.55 (0.35-0.88)| 0.012   |
| T vs C           |            |          | 0.82 (0.73-0.92)| 0.001   |
| rs10777373       |            |          |                |         |
| CC               | 472        | 513      | 1.00 (Reference)|         |
| TC               | 361        | 446      | 0.88 (0.73-1.06)| 0.179   |
| TT               | 67         | 119      | 0.61 (0.44-0.84)| 0.003   |
| T vs C           |            |          | 0.82 (0.73-0.94)| 0.003   |
| rs11588454       |            |          |                |         |
| TT               | 479        | 638      | 1.00 (Reference)|         |
| TC               | 360        | 388      | 1.24 (1.03-1.49)| 0.026   |
| CC               | 61         | 52       | 1.56 (1.06-2.30)| 0.023   |
| C vs T           |            |          | 1.25 (1.11-1.40)| 0.002   |
| rs11897825       |            |          |                |         |
| AA               | 286        | 409      | 1.00 (Reference)|         |
| AG               | 466        | 518      | 1.29 (1.06-1.57)| 0.012   |
| GG               | 148        | 151      | 1.40 (1.07-1.84)| 0.015   |
| G vs A           |            |          | 1.20 (1.09-1.32)| 0.001   |

* Adjusted for age, smoking status, family history of cancer and BMI.

morning preference and suggestive evidence for an adverse effect of increased sleep duration on BC risk [16]. However, OSAS trait was not evaluated due to the complexity of trait measurement. To make up for this defect, a two-sample MR method was implemented to evaluated the explore the causal relationships between OSAS and risk of BC in current study. Results of both of Chinese samples and the Asian
Table 3. Associations of the OSAS variants with BC risk in Chinese population.

| SNP            | OSAS cases | Controls | OR (95% CIs) * | P value |
|----------------|------------|----------|----------------|---------|
| rs10097555 AA  | 827        | 769      | 1.00 (Reference)| 0.032   |
| rs10097555 AG  | 351        | 395      | 0.83 (0.69-0.98)| 0.038   |
| rs10097555 GG  | 22         | 36       | 0.57 (0.33-0.97)| 0.007   |
| G vs A         |            |          | 0.82 (0.70-0.95)|         |
| rs11074782 CC  | 827        | 769      | 1.00 (Reference)| 0.032   |
| rs11074782 TC  | 341        | 395      | 0.83 (0.69-0.98)| 0.038   |
| rs11074782 TT  | 22         | 36       | 0.57 (0.33-0.97)| 0.007   |
| T vs C         |            |          | 0.82 (0.70-0.95)|         |
| rs10777373 CC  | 631        | 571      | 1.00 (Reference)| 0.032   |
| rs10777373 TC  | 461        | 498      | 0.83 (0.69-0.98)| 0.038   |
| rs10777373 TT  | 108        | 131      | 0.57 (0.33-0.97)| 0.007   |
| T vs C         |            |          | 0.82 (0.70-0.95)|         |
| rs11588454 CC  | 651        | 705      | 1.00 (Reference)| 0.032   |
| rs11588454 TC  | 461        | 498      | 0.83 (0.69-0.98)| 0.038   |
| rs11588454 TT  | 108        | 131      | 0.57 (0.33-0.97)| 0.007   |
| T vs C         |            |          | 0.82 (0.70-0.95)|         |
| rs11897825 AA  | 388        | 452      | 1.00 (Reference)| 0.032   |
| rs11897825 AG  | 611        | 583      | 1.22 (1.02-1.46)| 0.027   |
| rs11897825 GG  | 201        | 165      | 1.42 (1.11-1.82)| 0.005   |
| G vs A         |            |          | 1.19 (1.06-1.34)| 0.003   |

* Adjusted for age, smoking status, family history of cancer and BMI.

Table 4. Genetic variants used as instrumental variables in summary statistics approach.

| SNPs               | Effect allele | Beta (OSAS) | Se (OSAS) | Beta (BC) | Se (BC) |
|--------------------|---------------|-------------|-----------|-----------|---------|
| **Current study**  |               |             |           |           |         |
| rs10097555         | A             | 0.22        | 0.06      | 0.20      | 0.07    |
| rs11074782         | C             | 0.20        | 0.06      | 0.24      | 0.07    |
| rs10777373         | C             | 0.20        | 0.06      | 0.16      | 0.06    |
| rs11588454         | C             | 0.22        | 0.06      | 0.16      | 0.07    |
| rs11897825         | G             | 0.18        | 0.05      | 0.17      | 0.06    |
| **BCAC study (Asian population)** |               |             |           |           |         |
| rs10097555         | A             | 0.22        | 0.06      | 0.08      | 0.03    |
| rs11074782         | C             | 0.20        | 0.06      | 0.08      | 0.04    |
| rs10777373         | C             | 0.20        | 0.06      | 0.05      | 0.05    |
| rs11588454         | C             | 0.22        | 0.06      | 0.04      | 0.04    |
| rs11897825         | G             | 0.18        | 0.05      | 0.02      | 0.04    |

Population of the BCAC study revealed that OSAS has a causal effect on higher BC risk. This results supported the previous underpowered and inconsistent studies and provided stronger evidence for the carcinogenesis role of OSAS [23, 46–49]. We included five instrument SNPs, which were reported in previous genome-wide association studies (GWAS) and replicated in our Chinese samples, for the IV construction of OSAS [40, 51].

*In vitro* and *in vivo* experiments have provided many insights into the mechanism of hypoxia in the progress of carcinogenesis and tumor progression of breast
Table 5. Genetically predicted associations between OSAS and susceptibility of BC.

| MR methods        | Current study | BCAC study (Asian population) |
|-------------------|---------------|-------------------------------|
|                   | OR (95% CI)   | P value                       | OR (95% CI)   | P value |
| IVW               | 2.47 (1.86-3.27) | 3.6×10^{-10}                  | 1.33 (1.13-1.56) | 0.0006  |
| MBE               | 2.31 (1.34-4.01) | 2.7×10^{-3}                   | 1.42 (1.06-1.91) | 0.021   |
| Penalized IVW     | 2.47 (1.86-3.27) | 3.6×10^{-10}                  | 1.33 (1.13-1.56) | 0.0006  |
| Robust IVW        | 2.45 (1.89-3.16) | 8.4×10^{-12}                  | 1.33 (1.19-1.49) | 8.9×10^{-7} |
| Simple median     | 2.48 (1.53-4.03) | 2.3×10^{-4}                   | 1.28 (1.00-1.64) | 0.047   |
| Weighted median   | 2.43 (1.51-3.91) | 2.4×10^{-4}                   | 1.34 (1.06-1.70) | 0.013   |

cancer. Two main hypoxia markers, CAIX and HIF-1α, have been widely studied and were up-regulated in BC tissues using GEPIA 2 [52]. An HIF-1α/VEGF-A Axis in cytotoxic T cells was involved in the regulation of tumor progression, while loss of HIF-1α in CD8+ T cells could reduce tumor infiltration and tumor cell killing, and altered tumor vascularization [53]. A high amount of adipocytes enhanced BC progression due to the increased expression of HIF-1α [54]. Additionally, higher levels of serum CAIX was significant prognostic biomarkers of shorter PFS for BC, and CAIX could form a transport metabolon with monocarboxylate transporters in human breast cancer cells [55, 56].

This study has several methodological strengths. First, multiple samples to assess the causal effect of OSAS on BC risk. Second, rigor of the IV construction for OSAS. All five variants were GWAS identified and replicated in our samples. The F-statistic for the 5 instrument SNPs were all well above the threshold of F >10 typically recommended for MR analyses. Third, results were confirmed through sensitivity analyses and pleiotropy effect examination. Limitation should be also considered when interpret the results. First should be the limited number of IV variants. In current study, OSAS risk loci identified by GWASs mostly in European population were evaluated first in Chinese population. Only 5 variants replicated to be associated with OSAS in Chinese population. Next step, more GWASs of OSAS conducted in Asian population are needed. Second, shortage of a large-sample cohort limited the authority of evidence. Future large pooling consortia, larger GWAS of OSAS in Asian population and MR studies using individual level data are warranted.

CONCLUSIONS

In summary, this study provides novel evidence that genetically determined higher risk of OSAS has a causal effect on higher risk of BC. Our results, in combination with previous literature, provide evidence that population-wide screening for OSAS should be recommended as a primary BC prevention strategy. Future research should be best focused on understanding the mechanisms of the relationship between OSAS and breast carcinogenesis.

MATERIALS AND METHODS

Study population

In this two-sample MR study, ethical approval was obtained from the Ethical Committee of the Second Hospital of Shanxi Medical University, and all participants signed the informed consent. The determination of OSAS was conducted using an overnight laboratory-based polysomnography (PSG) test, together with the measurement of apnea–hypopnea index (AHI). Then, OSAS was defined as an AHI >5 events/h, and daytime symptoms specific for an OSAS. The diagnosis of BC was determined by histopathological examination. Demographic information was collected from the medical records. During the same period of time, healthy volunteers visiting the same hospital for physical examination were selected as controls. The shared controls was frequency matched by age, ethnicity and body mass index (BMI). Finally, 900 OSAS (1078 controls, 122 OSAS cases were excluded from the controls in this stage) and 1200 BC cases (1200 controls) were included in current study. Ten ml of venous blood was collected from each study subject. Besides, we also applied the summarized iCOGS data of Asian population (6269 BC cases; 6624 controls) from the Breast Cancer Association Consortium (BCAC) to validate our findings [57].

Variants selection and genotyping

In MR, genetic variants associated with a risk factor are used as IV to infer the true relationship between the risk factor and outcome. Using the GWAS identified loci to construct the IV was the most commonly used method, as the repeatability, accuracy and stability of the results [58]. In current study, we first retrieved the GWAS catalog, and 23 OSAS risk
loci were identified, mostly in European population (Supplementary Table 1). Then, the variants were filtered with the standard of minor allele frequency (MAF) ≥ 5% in Chinese Han population and pairwise r² < 0.8. Thirteen variants were kept. Further, genotyping was performed for these 13 SNPs using the TaqMan allelic discrimination assay on an ABI 7900 system (Applied Biosystems Inc, Foster City, CA, USA). Blind duplicates of 10% randomly selected samples were genotyped to verify the reproducibility of genotype calls; concordance between duplicates was greater than 100% for all pairs.

**Statistical analysis**

All statistical analyses were conducted using the R statistical software (version 3.6.1), and all P values are two-tailed, and P < 0.05 was considered significant. The associations of each SNP with OSAS and BC susceptibility were estimated by unconditional logistic regression analyses with odds ratios (ORs) and 95% confidence intervals (CIs).

We selected the random-effect inverse-variance weighted (IVW) method as the primary analyses. Furthermore, model based estimation (MBE), penalized IVW, robust IVW, simple median, and weighted median method were used for sensitivity analyses. We computed F-statistics to quantify the strength of the selected instruments. Besides, three methods were conducted to detect possible pleiotropy. First, we looked up the MR-Base (http://app.mrbase.org/), PhenoScanner database (http://www.phenoscaner.medschl.cam.ac.uk/) and the GWAS catalog (https://www.ebi.ac.uk/gwas/home) for potential associations of all 5 variants in our study with the following BC-related traits and risk factors. Second, we tested whether the intercept from MR-Egger regression differed from zero, which provided evidence of directional pleiotropy. Third, the MR-Pleiotropy Residual Sum and Outlier (MR-PRESSO) was used to identify and correct for potential outliers.

**AUTHOR CONTRIBUTIONS**

Guarantor of integrity of the entire study, study concepts and design, and manuscript review: Xiao-Ling Gao; Investigation: Zhi-Mei Jia, Fang-Fang Zhao, Dong-Dong An, Bei Wang, Er-Jing Cheng, Yan Chen, Jian-Nan Gong, Dai Liu, Ya-Qiong Huang, Jiao-Jiao Yang, Shu-Juan Wang.

**CONFLICTS OF INTEREST**

The authors declare no conflicts of interest.

**FUNDING**

The research leading to these results has received funding from the National Natural Science Foundation of China (No. 81870076), Research Project for Excellent Talents Supported by Department of science and technology of Shanxi Province (No.201805D211011) and International cooperative research and development project of Shanxi Science and Technology Department (No. 201703D421027). The funding bodies were not involved in the design of the study and collection, analysis, and interpretation of data or in writing the manuscript.

Funding for BCAC and iCOGS came from: Cancer Research UK [grant numbers C1287/A16563, C1287/A10118, C1287/A10710, C12292/A11174, C1281/A12014, C5047/A8384, C5047/A15007, C5047/A10692, C8197/A16565], the European Union’s Horizon 2020 Research and Innovation Programme (grant numbers 634935 and 633784 for BRIDGES and B-CAST respectively), the European Community’s Seventh Framework Programme under grant agreement n° 223175 [HEALTHF2-2009-223175] (COGS), the National Institutes of Health [CA128978] and Post-Cancer GWAS initiative [1U19 CA148537, 1U19 CA148065-01 (DRIVE) and 1U19 CA148112 - the GAME-ON initiative], the Department of Defence [W81XWH-10-1-0341], and the Canadian Institutes of Health Research CIHR) for the CIHR Team in Familial Risks of Breast Cancer [grant PSR-SIRI-701]. All studies and funders as listed in Michailidou K et al (2013 and 2015) and in Guo Q et al (2015) are acknowledged for their contributions.

**REFERENCES**

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin. 2019; 69:7–34. https://doi.org/10.3322/caac.21551 PMID:30620402

2. DeSantis CE, Ma J, Gaudet MM, Newman LA, Miller KD, Goding Sauer A, Jemal A, Siegel RL. Breast cancer statistics, 2019. CA Cancer J Clin. 2019; 69:438–51. https://doi.org/10.3322/caac.21583 PMID:31577379

3. Lee BL, Liedke PE, Barrios CH, Simon SD, Finkelstein DM, Goss PE. Breast cancer in Brazil: present status and future goals. Lancet Oncol. 2012; 13:e95–102. https://doi.org/10.1016/S1470-2045(11)70323-0 PMID:22381937

4. Fan L, Strasser-Weippl K, Li JJ, St Louis J, Finkelstein DM, Yu KD, Chen WQ, Shao ZM, Goss PE. Breast cancer in China. Lancet Oncol. 2014; 15:e279–89. https://doi.org/10.1016/S1470-2045(13)70567-9 PMID:24872111

5. Roth GA, Abate D, Abate KH, Abay SM, Abbafati C, Abbasi N, Abbastabar H, Abd-Allah F, Abdel J,
Abdelalim A, Abdollahpour I, Abdullahkader RS, Abebe HT, et al, and GBD 2017 Causes of Death Collaborators. Global, regional, and national age-sex-specific mortality for 282 causes of death in 195 countries, 1980-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018; 392:1736–88. https://doi.org/10.1016/S0140-6736(18)32203-7 PMID: 30496103

6. Martinez-Garcia MA, Campos-Rodriguez F, Almendros I, García-Rio F, Sanchez-de-la-Torre M, Farre R, Gozal D. Cancer and Sleep Apnea: Cutaneous Melanoma as a Case Study. Am J Respir Crit Care Med. 2019; 200:1345–53. https://doi.org/10.1164/rccm.201903-0577PP PMID: 31339332

7. Pataka A, Bonsignore MR, Ryan S, Riha RL, Pepin JL, Schiza S, Basoglu OK, Sliwinski P, Ludka O, Steiropoulos P, Anttalainen U, McNicholas WT, Hedner J, Grote L, and ESADA study group. Cancer prevalence is increased in females with sleep apnoea: data from the ESADA study. Eur Respir J. 2019; 53:1900091. https://doi.org/10.1183/13993003.00091-2019 PMID: 31109987

8. Haus E, Smolensky MH. Shift work and cancer risk: potential mechanistic roles of circadian disruption, light at night, and sleep deprivation. Sleep Med Rev. 2013; 17:273–84. https://doi.org/10.1016/j.smrv.2012.08.003 PMID: 23137527

9. LeVan TD, Xiao P, Kumar G, Kupzyk K, Qiu F, Klinkebiel D, Eudy J, Cowan K, Berger AM. Genetic Variants in Circadian Rhythm Genes and Self-Reported Sleep Quality in Women with Breast Cancer. J Circadian Rhythms. 2019; 17:6. https://doi.org/10.5334/jcr.184 PMID: 31303884

10. Li S, Ao X, Wu H. The role of circadian rhythm in breast cancer. Chin J Cancer Res. 2013; 25:442–50. https://doi.org/10.3978/j.issn.1000-9604.2013.08.19 PMID: 23997531

11. Keith LG, Oleśzcuk JJ, Laguens M. Circadian rhythm chaos: a new breast cancer marker. Int J Fertil Womens Med. 2001; 46:238–47. PMID: 11720196

12. Burki TK. Night shift work and breast cancer. Lancet Oncol. 2019; 20:e352. https://doi.org/10.1016/S1470-2045(19)30383-3 PMID: 31178375

13. Pahwa M, Labrèche F, Demers PA. Night shift work and breast cancer risk: what do the meta-analyses tell us? Scand J Work Environ Health. 2018; 44:432–35. https://doi.org/10.5271/sjweh.3738 PMID: 29790566

14. Hansen J. Night Shift Work and Risk of Breast Cancer. Curr Environ Health Rep. 2017; 4:325–39. https://doi.org/10.1007/s40572-017-0155-y PMID: 28770538

15. Samulin Erdem J, Notø HO, Skare Ø, Lie JS, Petersen-Øverleir M, Reszka E, Peplonska B, Zienolldiny S. Mechanisms of breast cancer risk in shift workers: association of telomere shortening with the duration and intensity of night work. Cancer Med. 2017; 6:1988–97. https://doi.org/10.1002/cam4.1135 PMID: 28707432

16. Richmond RC, Anderson EL, Dashi HS, Jones SE, Lane JM, Strand LB, Brumpton B, Rutter MK, Wood AR, Straif K, Relton CL, Munafò M, Frayling TM, et al. Investigating causal relations between sleep traits and risk of breast cancer in women: mendelian randomisation study. BMJ. 2019; 365:l2327. https://doi.org/10.1136/bmj.l2327 PMID: 31243001

17. Farré N, Farré R, Gozal D. Sleep Apnea Morbidity: A Consequence of Microbial-Immune Cross-Talk? Chest. 2018; 154:754–59. https://doi.org/10.1016/j.chest.2018.03.001 PMID: 29548630

18. Marhuenda E, Campillo N, Gabasa M, Martínez-García MA, Campos-Rodríguez F, Gozal D, Navajas D, Alcaraz J, Farré R, Almendros I. Effects of Sustained and Intermittent Hypoxia on Human Lung Cancer Cells. Am J Respir Cell Mol Biol. 2019; 61:540–44. https://doi.org/10.1016/j.rcmb.2018.0412LE PMID: 31573339

19. Yoon DW, Kim YS, Hwang S, Khalmuratova R, Lee M, Kim JH, Lee GY, Koh SJ, Park JW, Shin HW. Intermittent hypoxia promotes carcinogenesis in azoxymethane and dextran sodium sulfate-induced colon cancer model. Mol Carcinog. 2019; 58:654–65. https://doi.org/10.1002/mc.22957 PMID: 30575123

20. Kukwa W, Migacz E, Druc K, Grzesiuk E, Czarnecka AM. Obstructive sleep apnea and cancer: effects of intermittent hypoxia? Future Oncol. 2015; 11:3285–98. https://doi.org/10.2217/fon.15.216 PMID: 26562000

21. Seijo LM, Pérez-Warnisher MT, Giraldo-Cadavid LF, Oliveros H, Cabezas E, Troncoso MF, Gómez T, Melchor R, Pinillos EJ, El Hachem A, Gotera C, Rodriguez P, González-Mangado N, Peces-Barba G. Obstructive sleep apnea and nocturnal hypoxemia are associated with an increased risk of lung cancer. Sleep Med. 2019; 63:41–45. https://doi.org/10.1016/j.sleep.2019.05.011 PMID: 31605903

22. Sillah A, Watson NF, Schwartz SM, Gozal D, Phipps AI. Sleep apnea and subsequent cancer incidence. Cancer Causes Control. 2018; 29:987–94. https://doi.org/10.1007/s10552-017-0987-2
23. Gozal D, Ham SA, Mokhlesi B. Sleep Apnea and Cancer: Analysis of a Nationwide Population Sample. Sleep. 2016; 39:1493–500. https://doi.org/10.5665/sleep.6004 PMID:27166241
24. Martínez-García MA, Campos-Rodriguez F, Almendros I, Farré R. Relationship Between Sleep Apnea and Cancer. Arch Bronconeumol. 2015; 51:456–61. https://doi.org/10.1016/j.arbr.2015.02.034 PMID:25843225
25. Palmer TM, Lawlor DA, Harbord RM, Sheehan NA, Tobias JH, Timpson NJ, Davey Smith G, Sterne JA. Using multiple genetic variants as instrumental variables for modifiable risk factors. Stat Methods Med Res. 2012; 21:223–42. https://doi.org/10.1177/0962280210394459 PMID:21216802
26. Dale CE, Fatemifar G, Palmer TM, White J, Prieto-Merino D, Zabaneh D, Engmann JE, Shah T, Wong A, Warren HR, McLachlan S, Trompet S, Moldovan M, et al, and UCLEB Consortium; METASTROKE Consortium. Causal Associations of Adiposity and Body Fat Distribution With Coronary Heart Disease, Stroke Subtypes, and Type 2 Diabetes Mellitus: A Mendelian Randomization Analysis. Circulation. 2017; 135:2373–88. https://doi.org/10.1161/CIRCULATIONAHA.116.026560 PMID:28500271
27. Emdin CA, Khera AV, Kathiresan S. Mendelian Randomization. JAMA. 2017; 318:1925–26. https://doi.org/10.1001/jama.2017.17219 PMID:29164242
28. Carter AR, Gill D, Davies NM, Taylor AE, Tillmann T, Vaucher J, Wootten RE, Munafő MR, Hemani G, Malik R, Seshadri S, Woo D, Burgess S, et al. Understanding the consequences of education inequality on cardiovascular disease: mendelian randomisation study. BMJ. 2019; 365:i1855. https://doi.org/10.1136/bmj.i1855 PMID:31122926
29. Cerani A, Zhou S, Forgetta V, Morris JA, Trajanoska K, Rivadeneira F, Larsson SC, Michaëlsson K, Richards JB. Genetic predisposition to increased serum calcium, bone mineral density, and fracture risk in individuals with normal calcium levels: mendelian randomisation study. BMJ. 2019; 366:l4410. https://doi.org/10.1136/bmj.l4410 PMID:31371314
30. Long T, Wang J, Han X, Wang F, Hu H, Yu C, Yuan J, Yao P, Wei S, Wang Y, Liang Y, Miao X, Zhang X, et al. Association between resting heart rate and incident diabetes risk: a Mendelian randomization study. Acta Diabetol. 2019; 56:1037–44.
31. Zhao JV, Kwok MK, Schooling CM. Effect of glutamate and aspartate on ischemic heart disease, blood pressure, and diabetes: a Mendelian randomization study. Am J Clin Nutr. 2019; 109:1197–206. https://doi.org/10.1093/ajcn/nqy362 PMID:30949673
32. Ference BA, Ray KK, Catapano AL, Ference TB, Burgess S, Neff DR, Oliver-Williams C, Wood AM, Butterworth AS, Di Angelantonio E, Danesh J, Kastelein JJ, Nicholls SI. Mendelian Randomization Study of ACLY and Cardiovascular Disease. N Engl J Med. 2019; 380:1033–42. https://doi.org/10.1056/NEJMoa1806747 PMID:30865797
33. Goto A, Yamaji T, Sawada N, Momozawa Y, Kamatani Y, Kubo M, Shimazu T, Inoue M, Noda M, Tsugane S, Iwasaki M. Diabetes and cancer risk: A Mendelian randomization study. Int J Cancer. 2020; 146:712–719. https://doi.org/10.1002/ijc.32310 PMID:30927373
34. Zhang B, Shu XO, Delahanty RJ, Zeng C, Michailidou K, Bolla MK, Wang Q, Dennis J, Wen W, Long J, Li C, Dunning AM, Chang-Claude J, et al, and kConFab Investigators, Australian Ovarian Study Group, and DRIVE Project. Height and Breast Cancer Risk: Evidence From Prospective Studies and Mendelian Randomization. J Natl Cancer Inst. 2015; 107:dvj219. https://doi.org/10.1093/jnci/dvj219 PMID:26296642
35. Vorona RD, Ware JC. History and epidemiology of sleep-related breathing disorders. Oral Maxillofac Surg Clin North Am. 2002; 14:273–83. https://doi.org/10.1016/S1042-0188(01)80105-0 PMID:18088629
36. Stradling JR. Sleep-related breathing disorders. 1. Obstructive sleep apnoea: definitions, epidemiology, and natural history. Thorax. 1995; 50:683–89. https://doi.org/10.1136/thx.50.6.683 PMID:7638816
37. Bresnitz EA, Goldberg R, Kossini RM. Epidemiology of obstructive sleep apnea. Epidemiol Rev. 1994; 16:210–27. https://doi.org/10.1093/oxfordjournals.epirev.a036151 PMID:7713177
38. Franklin KA, Lindberg E. Obstructive sleep apnea is a common disorder in the population-a review on the epidemiology of sleep apnea. J Thorac Dis. 2015; 7:1311–22. https://doi.org/10.3978/j.issn.2072-1439.2015.06.11 PMID:26380759
39. Valipour A. Gender-related differences in the obstructive sleep apnea syndrome. Pneumologie. 2012; 66:584–88.
40. Sillah A, Watson NF, Gozal D, Phipps AI. Obstructive sleep apnea severity and subsequent risk for cancer incidence. Prev Med Rep. 2019; 15:100886. https://doi.org/10.1016/j.pmedr.2019.100886 PMID:31193286

41. Gozal D, Farré R, Nieto FJ. Obstructive sleep apnea and cancer: epidemiologic links and theoretical biological constructs. Sleep Med Rev. 2016; 27:43–55. https://doi.org/10.1016/j.smrv.2015.05.006 PMID:26447849

42. Gozal D, Farré R, Nieto FJ. Putative Links Between Sleep Apnea and Cancer: From Hypotheses to Evolving Evidence. Chest. 2015; 148:1140–47. https://doi.org/10.1378/chest.15-0634 PMID:26020135

43. Chang WP, Liu ME, Chang WC, Yang AC, Ku YC, Pai JT, Lin YW, Tsai SJ. Sleep apnea and the subsequent risk of breast cancer in women: a nationwide population-based cohort study. Sleep Med. 2014; 15:1016–20. https://doi.org/10.1016/j.sleep.2014.05.026 PMID:25085620

44. Stern TP, Auckley D. Obstructive sleep apnea following treatment of head and neck cancer. Ear Nose Throat J. 2007; 86:101–03. https://doi.org/10.1177/014556130708600214 PMID:17385619

45. Qian W, Haight J, Poon I, Enepekides D, Higgins KM. Sleep apnea in patients with oral cavity and oropharyngeal cancer after surgery and chemoradiation therapy. Otolaryngol Head Neck Surg. 2010; 143:248–52. https://doi.org/10.1016/j.otohns.2010.02.032 PMID:20647129

46. Kendzerska T, Leung RS, Hawker G, Tomlinson G, Gershon AS. Obstructive sleep apnea and the prevalence and incidence of cancer. CMAJ. 2014; 186:985–92. https://doi.org/10.1503/cmaj.140238 PMID:25096668

47. Brenner R, Kivity S, Peker M, Reinhold D, Keinan-Boker L, Silverman B, Liphsitz I, Kolitz T, Levy C, Shlomi D, Pillar G, Peled N. Increased Risk for Cancer in Young Patients with Severe Obstructive Sleep Apnea. Respiration. 2019; 97:15–23. https://doi.org/10.1159/000486577 PMID:30419556

48. Campos-Rodriguez F, Martinez-Garcia MA, Martinez M, Duran-Cantolla J, Peña ML, Masdeu MJ, Gonzalez M, Campo F, Gallego I, Marin JM, Barbe F, Montserrat JM, Farre R, and Spanish Sleep Network. Association between obstructive sleep apnea and cancer incidence in a large multicenter Spanish cohort. Am J Respir Crit Care Med. 2013; 187:99–105. https://doi.org/10.1164/rccm.201209-1671OC PMID:23155146

49. Lee S, Kim BG, Kim JW, Lee KL, Koo DL, Nam H, Im JP, Kim JS, Koh SJ. Obstructive sleep apnea is associated with an increased risk of colorectal neoplasia. Gastrointest Endosc. 2017; 85:568–573.e1. https://doi.org/10.1016/j.gie.2016.07.061 PMID:27506392

50. Baik I, Seo HS, Yoon D, Kim SH, Shin C. Associations of Sleep Apnea, NRG1 Polymorphisms, Alcohol Consumption, and Cerebral White Matter Hyperintensities: Analysis with Genome-Wide Association Data. Sleep. 2015; 38:1137–43. https://doi.org/10.5665/sleep.4830 PMID:25325441

51. Cade BE, Chen H, Stilp AM, Gleason KJ, Sofer T, Ancoli-Israel S, Arens R, Bell GI, Below JE, Bjonnes AC, Chun S, Conomos MP, Evans DS, et al. Genetic Associations with Obstructive Sleep Apnea Traits in Hispanic/Latino Americans. Am J Respir Crit Care Med. 2016; 194:886–97. https://doi.org/10.1164/rccm.201512-2431OC PMID:26977737

52. Tang Z, Kang B, Li C, Chen T, Zhang Z. GEPIA2: an enhanced web server for large-scale expression profiling and interactive analysis. Nucleic Acids Res. 2019; 47:W556–60. https://doi.org/10.1093/nar/gkz430 PMID:31114875

53. Palazon A, Tyarakis PA, Macias D, Velica P, Rundqvist H, Fitzpatrick S, Vojnovic N, Phan AT, Loman N, Hedenfalk I, Hatschek T, Lövrot J, Foukakis T, et al. An HIF-1α/VEGF-A Axis in Cytotoxic T Cells Regulates Tumor Progression. Cancer Cell. 2017; 32:669–683.e5. https://doi.org/10.1016/j.ccell.2017.10.003 PMID:29136509

54. Rausch LK, Netzer NC, Hoegel J, Pramsohler S. The Linkage between Breast Cancer, Hypoxia, and Adipose Tissue. Front Oncol. 2017; 7:211. https://doi.org/10.3389/fonc.2017.00211 PMID:28993797

55. Ames S, Andring JT, McKenna R, Becker HM. CAIX forms a transport metabolon with monocarboxylate transporters in human breast cancer cells. Oncogene. 2020: 39:1710-1723. https://doi.org/10.1038/s41388-019-1098-6 PMID:31723238

56. Ho D, Huang J, Chapman JW, Leitzel K, Ali SM, Shepherd L, Parulekar WR, Ellis CE, Crescnzo RJ, Zhu L, Virk S, Nomikos D, Aparicio S, et al. Impact of serum HER2, TIMP-1, and CAIX on outcome for HER2+ metastatic breast cancer patients: CCTG
57. Michailidou K, Beesley J, Lindstrom S, Canisius S, Dennis J, Lush MJ, Maranian MJ, Bolla MK, Wang Q, Shah M, Perkins BJ, Czene K, Eriksson M, et al, and BOCS, and kConFab Investigators, and AOCS Group, and NBCS, and GENICA Network. Genome-wide association analysis of more than 120,000 individuals identifies 15 new susceptibility loci for breast cancer. Nat Genet. 2015; 47:373–80.

58. Swerdlow DI, Kuchenbaecker KB, Shah S, Sofat R, Holmes MV, White J, Mindell JS, Kivimaki M, Brunner EJ, Whittaker JC, Casas JP, Hingorani AD. Selecting instruments for Mendelian randomization in the wake of genome-wide association studies. Int J Epidemiol. 2016; 45:1600–16.

https://doi.org/10.1093/ije/dyw088 PMID: 27342221
SUPPLEMENTARY MATERIALS

Supplementary Table

Please browse Full Text version to see the data of Supplementary Table 1

Supplementary Table 1. GWAS loci for obstructive sleep apnea in GWAS catalog.