Obstructive sleep apnea (OSA) is a prevalent form of sleep-disordered breathing. OSA is known to be associated with multiple cardiovascular outcomes, including hypertension, coronary artery disease, stroke, and type 2 diabetes. Numerous in-vitro and murine studies have also suggested that hypoxia plays a notable role in tumor formation, progression and metastasis.

However, epidemiological studies have reported conflicting findings on this relationship.

**Methods**

- PubMed, Embase, Scopus and Cochrane Library were systematically searched for observational studies published from inception to 15 November 2020, in adults aged ≥18 years, reporting objective measurements or clinical diagnosis of sleep apnea and the association with incident breast cancer.
- Maximal covariate-adjusted hazard ratios (HR) were extracted and pooled using the generic inverse variance method and random effects model on RevMan.
- A pre-specified subgroup analysis for studies with median duration ≥ five years was performed. Two reviewers independently assessed risk of bias using the Newcastle-Ottawa Scale (NOS).

**Background**

- Obstructive sleep apnea (OSA) is a prevalent form of sleep-disordered breathing.
- OSA is known to be associated with multiple cardiovascular outcomes, including hypertension, coronary artery disease, stroke, and type 2 diabetes.
- Numerous in-vitro and murine studies have also suggested that hypoxia plays a notable role in tumor formation, progression and metastasis.
- However, epidemiological studies have reported conflicting findings on this relationship.

**Figure 1: PRISMA Flow Chart**

**Figure 2: Baseline characteristics of studies**

**Results**

**Meta-analysis**

- Seven studies assessing the relationship between OSA and breast cancer risk were included for overall analysis in our meta-analysis.
- The combined effect estimations (HRs) using random-effects model are presented in Fig. 3. The overall results suggest a statistically significant 43% increase in breast cancer risk (combined HR: 1.43; 95% CI: 1.05-1.94) in OSA patients.
- We found statistically significant heterogeneity across the included studies (I²=95%, p<0.00001). After excluding one paper which was not multi-adjusted, subsequent analysis yielded a statistically significant association (combined HR: 1.43; 95% CI: 1.25-1.64), which was similar to the overall analysis.
- Subgroup analysis was performed based on the median duration of follow-up (follow-up ≥ five years).
- The results of subgroup analysis are shown in Fig. 4. In the subgroup analysis, a greater statistically significant association was observed in studies with follow-up ≥ five years (combined HR: 1.74; 95% CI: 1.10-2.7; I²=90%, p<0.0001).

**Systemic review**

- We included one study assessing the association between nocturnal hypoxaemia measured by sleep duration with arterial oxygen saturation <90% (1906) and breast cancer incidence. This study found that in patients with mild nocturnal hypoxaemia, the risk of breast cancer incidence was significantly elevated (adjusted HR: 2.04; 95% CI: 1.05-3.98). However, this significant positive association did not hold true for those with moderate (adjusted HR: 1.40; 95% CI: 0.69-2.87) and severe nocturnal hypoxaemia (adjusted HR: 1.14; 95% CI: 0.50-2.58). There were no studies linking other measures of OSA such as the Apnea Hypopnea Index and Oxygen Desaturation Index to breast cancer risk.
- We included a Mendelian randomization study investigating the cancer-inducing effect of genetically determined higher risk of OSA on breast cancer risk. This study found a significant positive association (OR: 2.47 for breast cancer risk per log-odds increment in OSA risk; 95% CI: 1.86-3.27) between genetic risk for OSA and breast cancer risk.

**Pathogenesis**

- Hypoxia causes increased expression of hypoxia-inducible factor-1 and 2 (HIF-1 and HIF-2) which upregulate pro-angiogenic pathways.
- Modified tissue environment may select for stem-like breast cancer cell populations which can survive periods of hypoxia and increase capacity for tumor growth. Intratumoral hypoxia may increase risk of haematogenous tumor metastasis.
- Hypoxia may be associated with a more aggressive breast cancer phenotype.

**Causal relationship**

Our meta-analysis findings are supported by a recent well-conducted Mendelian randomisation study. This study showed that genetically determined higher risk of OSA had a causal effect on higher risk of breast cancer, with two-fold increased odds of breast cancer in OSA patients.

**Confounders**

Potential confounders include: obesity, 14,25 diabetes, 26 smoking, 25,26 age, 25 sex, 25 and hypertension. 25 Out of the seven included studies in the meta-analysis, all adjusted for age and sex, four adjusted for type 2 diabetes mellitus and obesity, and three adjusted for alcohol use and hypertension.

**Discussion**

- This meta-analysis suggests that OSA increases the risk of breast cancer incidence, especially ≥ five years after OSA diagnosis.
- Intermittent hypoxia may play a role and further studies are needed to define its role, as well as to determine the differential risk of breast cancer in relation to OSA severity.
- Clinical triads are needed to assess the potential of timely OSA treatment in reducing the risk of breast cancer.
- Earlier screening of patients with current or past history of OSA may allow timely diagnosis and thus, better prognosis of breast cancer.