

## Systematic Meta-Analysis

# Is Shift Work Associated with Pancreatic Cancer? A Systematic Review and Meta-Analysis

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### Abstract

**Objectives:** Pancreatic cancer (PaC) is a highly fatal disease that can be influenced by occupational factors. Shift work has been suggested to be carcinogenic, yet little is known about its association with PaC. Herein, we performed this systematic review and meta-analysis to investigate the potential association between shift work and PaC.

**Methods:** We systematically searched PubMed and Scopus databases for eligible studies. The pooled hazard ratio (HR) and 95% confidence interval (CI) of PaC risk were calculated for those who had engaged in shift work. We used the  $I^2$  statistic to measure heterogeneity across studies and the test for funnel plot asymmetry to assess publication bias.

**Results:** This meta-analysis incorporated five studies involving participants from various regions, including Japan, the United States, Denmark, Sweden, and Germany. Combined, shift work was not associated with PaC: HR (95% CI) = 1.05 (0.91, 1.20). Neither heterogeneity across studies ( $I^2=0.0\%$  and  $p$ -heterogeneity = 0.913) nor publication bias ( $z=-0.276$  and  $p$ -publication bias=0.783) was detected. The results remained consistent in both sexes and PaC incidence and mortality.

**Conclusion:** Shift work does not seem to elevate the risk of PaC.

**Keywords:** Meta-analysis, pancreatic cancer, shift work, systematic review.

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Pancreatic cancer (PaC) is a formidable adversary in the realm of oncology, known for its aggressive nature and limited treatment options. Over the years, researchers have sought to uncover potential risk factors for this fatal disease. Smoking, diabetes, excessive alcohol consumption, obesity, and dietary factors are among these risk factors, suggesting that improving lifestyle could minimize PaC risk.<sup>[1]</sup>

A growing body of evidence has indicated that work conditions could contribute to the development of various cancers,<sup>[2]</sup> including PaC.<sup>[3]</sup> Among the various occupational

factors under scrutiny, shift work has garnered particular attention.<sup>[4-6]</sup> Shift work typically involves working outside of the traditional 6 a.m.-6 p.m. schedule, including evening, night, and rotating shifts. Healthcare, manufacturing, transportation, and emergency services are just a few sectors where shift work is prevalent. The International Agency for Research on Cancer (IARC) has classified night shift work as a probable carcinogen.<sup>[7]</sup> Shift work is associated with circadian rhythm disruption,<sup>[8]</sup> melatonin suppression attributed to exposure to light at night,<sup>[9]</sup> and reduced vita-

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min D levels due to lack of exposure to sunlight,<sup>[10]</sup> factors that could be related to cancer development.<sup>[7]</sup>

Some studies investigated the association between shift work and PaC risk;<sup>[11–17]</sup> however, they were limited by the small number of PaC cases, which weakened their statistical power. We, therefore, conducted a systematic review of cohort studies investigating the association between shift work and PaC risk before combining the results of eligible studies into a meta-analysis.

## Methods

We reported this meta-analysis according to the checklists of Meta-analysis Of Observational Studies in Epidemiology (MOOSE)<sup>[18]</sup> and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA).<sup>[19]</sup> However, the meta-analysis protocol was not registered in online review registries.

### Literature Search

Both authors independently searched PubMed and Scopus databases for potential studies published in English before the 4<sup>th</sup> of September 2023, using the following terms: ((Shift work) OR (Night work)) AND (Cancer) (Supplementary Table 1). We also conducted a manual search of the reference sections of retrieved original and review articles to search for other studies.

### Eligibility Criteria

Our eligibility criteria included: 1) shift work was the exposure, 2) PaC was the outcome, and 3) the study had a cohort design. No limitations were set regarding the year of publication. We exerted no effort to retrieve unpublished data. Besides, studies in languages other than English were not sought.

### Data Extraction

We extracted the following information from the included studies: publication year and place, number of participants, definitions of shift work and PaC, and variables included in the most adjusted regression models.

### Risk of Bias Assessment

The quality of studies was determined per the modified Newcastle–Ottawa Scale (NOS) in terms of studies' selection, comparability, and outcome.<sup>[20]</sup> The disagreements in assessing quality and risk of bias were resolved by discussion.

### Statistical Analysis

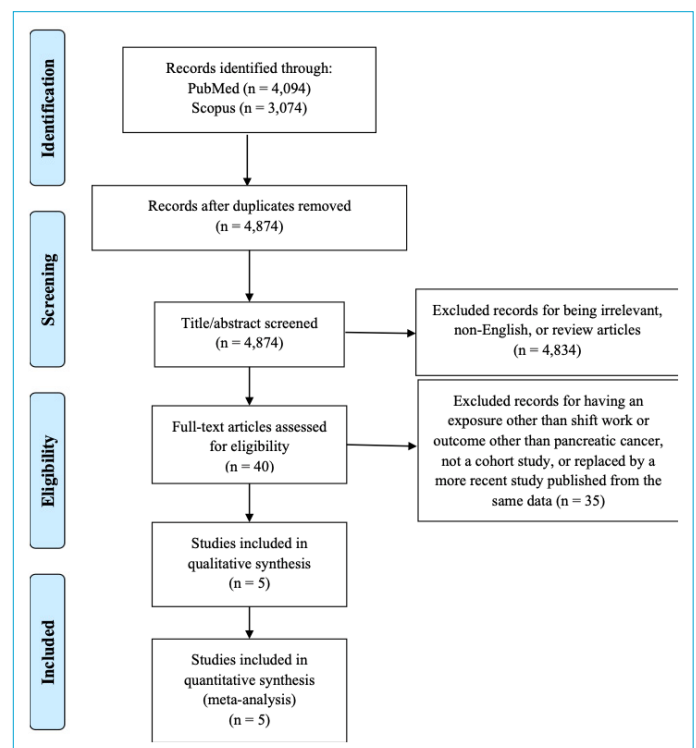
Given the variations in the definition of shift work across studies, we used the random-effects model to compute pooled HR and 95% CI of PaC among shift workers.<sup>[21]</sup> We also applied  $I^2$  statistics to examine the statistical heterogeneity across studies and the regression test for funnel plot asymmetry to assess publication bias.<sup>[22,23]</sup> We repeated the

meta-analysis after adding a case-control study that was omitted from the primary meta-analysis by our eligibility criteria.<sup>[16]</sup> Additionally, we investigated the association by sex and PaC definition (incidence versus mortality). R-3.2.0 statistical package (Metafor: A Meta-Analysis Package for R) was used for analysis.

## Results

Seven studies investigated the association between shift work and PaC. However, the Parent et al.<sup>[16]</sup> study was excluded from the primary meta-analysis because it had a case-control design. We also excluded the Lin et al.<sup>[17]</sup> study, which investigated PaC mortality among Japanese men, because a more recent study used the same data to investigate PaC incidence in both sexes.<sup>[11]</sup> Eventually, five studies were included (Fig. 1).

The five studies investigated participants from Japan, the US, Denmark, Sweden, and Germany (published between 2007 and 2021).<sup>[11–15]</sup> Two studies included men and women,<sup>[11,14]</sup> two studies included women only,<sup>[12,13]</sup> and one study included men only.<sup>[15]</sup> Besides, three studies investigated PaC incidence<sup>[11,14,15]</sup> and two studies investigated PaC mortality.<sup>[12,13]</sup> Four studies calculated HRs,<sup>[11–13,15]</sup> and one study calculated the standardized incidence ratio (Table 1).<sup>[14]</sup> All studies were of average to high quality per the modified NOS (Table 2).



**Figure 1.** PRISMA Flowchart of the selection process of the studies included in this meta-analysis.

**Table 1.** Summary of the studies included in the meta-analysis

Study ID	Population	Exposure	Outcome	Adjusted variables
Arafa et al. <sup>[11]</sup> Japan	45,390 men and women from the JACC Study Follow-up: 14.2 years (median)	Rotating shift vs. fixed day work (engaged in for longest occupation)	Pancreatic cancer incidence	Age, body mass index, education, employment, stress, smoking, alcohol, physical activity, walking, family history of cancer, intakes of protein, fat, and total energy, age at menarche, age at first birth, and menopause
Gu et al. <sup>[12]</sup> US	74,862 women from the Nurses' Health Study Follow-up: 22 years (maximum)	Night shift $\geq 15$ years vs. never	Pancreatic cancer mortality	Age, alcohol, physical exercise, menopause, postmenopausal hormone use, attending physical examination in the past 2 years, healthy eating score, smoking, pack-years, body mass index, and husband's education
Jørgensen et al. <sup>[13]</sup> (2007) Denmark	28,731 women from the Danish Nurse Cohort Follow-up: 17.6 years (mean)	Rotating vs. day shift (normal work)	Pancreatic cancer mortality	Age, smoking, pack-years, physical activity, body mass index, alcohol, diet (vegetables, fruit, and fatty meat), pre-existing diseases (hypertension, diabetes, and myocardial infarction), self-reported health, stressful work environment, marital status, and female reproductive factors (birth and use of hormone therapy and oral contraceptives)
Schwartzbaum et al. <sup>[14]</sup> (2017) Sweden	2,102,126 men and 1,148,661 women from the 1960 and 1970 Swedish censuses	Rotating shift work vs. total population	Pancreatic cancer incidence	Age, socioeconomic status, occupational position, and county of residence
Yong et al. <sup>[15]</sup> (2021) Germany	27,828 men in a large chemical industry Follow-up: 10 years (maximum)	Rotating shift vs. day work	Pancreatic cancer incidence	Age, job level, cigarette smoking, and employment duration

**Table 2.** Bias assessment using the Newcastle-Ottawa Quality Assessment Scale

Items	Arafa et al. <sup>[11]</sup> (2021)	Gu et al. <sup>[12]</sup> (2015)	Jørgensen et al. <sup>[13]</sup> (2007)	Schwartzbaum et al. <sup>[14]</sup> (2017)	Yong et al. <sup>[15]</sup> (2021)
Representativeness of the exposed cohort	*	*	*	*	*
Ascertainment of exposure	*	*	*	*	*
Selection of the non-exposed cohort	*	*	*	*	*
Demonstration that the outcome of interest was not present at the start of the study	*	*	*	*	*
Comparability	*	*	*	--	*
Assessment of outcome	*	*	*	*	*
Follow-up was long enough for outcomes to occur	*	*	*	*	*
Adequacy of follow-up of cohorts	*	*	*	--	--
Overall (total number of asterisks)	8	8	8	6	7

The possible overall scores range between 0 and 9.

Combined, shift work was not associated with PaC: HR (95% CI) =1.05 (0.91, 1.20) with no heterogeneity across studies ( $I^2=0.0\%$  and p-heterogeneity =0.913) (Fig. 2). No publication bias was detected ( $z=-0.276$  and p-publication bias =0.783) (Fig. 3).

The results remained consistent across sexes: HRs (95% CIs) =1.07 (0.91, 1.26) in men and 0.96 (0.72, 1.28) in women. Similarly, the result did not change by PaC definition: HRs (95% CIs) =1.07 (0.92, 1.25) in PaC incidence and 0.92 (0.63, 1.33) in PaC mortality (Table 3). Furthermore, including the case-control study by Parent et al.<sup>[16]</sup> did not affect the conclusion (Supplement Fig. 1).

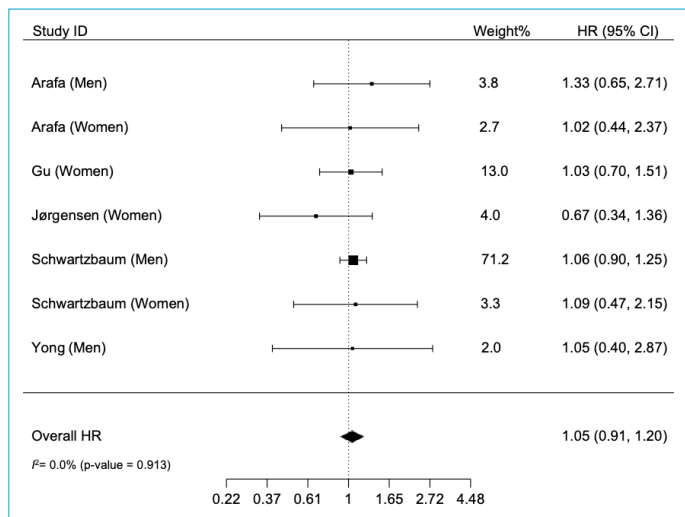
**Discussion**

Our study showed no association between shift work and PaC risk. No signs of heterogeneity across studies or publication bias were detected. The results did not materially

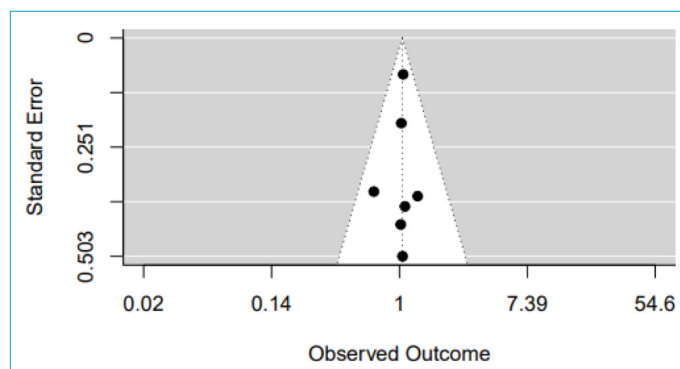
change by sex or PaC definition. Our results align with a previous meta-analysis that showed no excess risk of PaC among night-shift workers.<sup>[24]</sup>

Contrary to our findings, a case-control study including 94 PaC cases and 512 controls from Quebec reported that night work was associated with higher odds of PaC: odds ratio (95% CI) =2.27 (1.24, 4.15). The association was distributed by the cumulative duration of night work as follows: 1.91 (0.81, 4.52) for <5 years, 2.77 (0.97, 7.90) for 5-10 years, and 2.43 (0.91, 6.47) for >10 years.<sup>[16]</sup> However, when we included this study in our meta-analysis, the overall results did not materially change.

Of note, shift work has been linked to other cancers. A meta-analysis of 26 studies indicated increased breast cancer in females by 13% in short-term night-shift workers (<10 years) and 8% in long-term night-shift workers ( $\geq 10$  years).<sup>[25]</sup> Another meta-analysis of 33 studies showed that female shift workers had a 20% higher risk of breast cancer, especially receptor-positive breast cancer: 35% for estrogen receptor, 30% for progesterone receptor, and 42% for human epidermal growth factor receptor 2.<sup>[26]</sup> Among



**Figure 2.** The association between shift work and pancreatic cancer.



**Figure 3.** Funnel plot of the studies investigating the association between shift work and pancreatic cancer.

**Table 3.** The association between shift work and pancreatic cancer by sex and pancreatic cancer definition.

Categories	Number	HR (95% CI)
Men	3	1.07 (0.91, 1.26)
Women	4	0.96 (0.72, 1.28)
Pancreatic cancer incidence	5	1.07 (0.92, 1.25)
Pancreatic cancer mortality	2	0.92 (0.63, 1.33)

a total of 31 prospective cohort studies, incident breast cancer in females who reported night-shift work was only 3% higher than standard day workers, yet the association was statistically significant.<sup>[27]</sup> However, these findings were challenged by a recent meta-analysis that detected no association between shift work and breast cancer.<sup>[24]</sup> On the other hand, a meta-analysis of 15 studies detected a 23% rise in the risk of prostate cancer among male shift workers.<sup>[28]</sup> Another meta-analysis, including eight studies, reached almost the same conclusion.<sup>[29]</sup> However, more recent meta-analyses failed to detect a statistically significant association between shift work and prostate cancer.<sup>[24,30]</sup>

Although our meta-analysis provided a comprehensive overview of the association between shift work and PaC risk, some limitations should be considered. First, a limited number of studies were included. Second, the variation in shift work definitions across studies might hide misclassification bias. Besides, most studies did not provide data about the duration of shift work; therefore, we were not able to perform a dose-response meta-analysis. Third, because of the observational design of the included studies, the presence of undetected confounders is possible.

## Conclusion

This systematic review summarized the currently available epidemiological evidence on the association between shift work and PaC. After combining the results of the studies identified in a meta-analysis, we did not observe a statistically significant association between shift work and PaC risk. Our findings did not support the hypothesis that shift work could elevate the risk of PaC.

## Disclosures

**Peer-review:** Externally peer-reviewed.

**Conflict of Interest:** None declared.

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**Authorship Contributions:** Concept: A.A.; Design – A.A.; Supervision: A.A.; Materials: A.A., M.E.; Data collection and processing: A.A., M.E.; Analysis and interpretation: A.A.; Literature search: A.A., M.E.; Writing: A.A.; Critical Review: A.A., M.E.

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### Supplementary Table 1. PubMed search strategy

Search: ((Shift work) OR (Night work)) AND (Cancer)

((("shift"[All Fields] OR "shifted"[All Fields] OR "shifting"[All Fields] OR "shiftings"[All Fields] OR "shifts"[All Fields]) AND ("work"[MeSH Terms] OR "work"[All Fields])) OR (("night"[All Fields] OR "night s"[All Fields] OR "nights"[All Fields]) AND ("work"[MeSH Terms] OR "work"[All Fields]))) AND ("cancer s"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields])

#### Translations

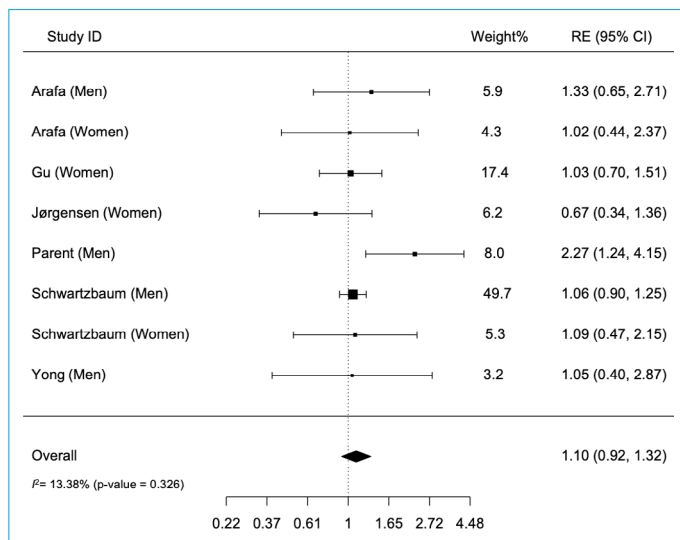
Shift: "shift"[All Fields] OR "shifted"[All Fields] OR "shifting"[All Fields] OR "shiftings"[All Fields] OR "shifts"[All Fields]

work: "work"[MeSH Terms] OR "work"[All Fields]

Night: "night"[All Fields] OR "night's"[All Fields] OR "nights"[All Fields]

work: "work"[MeSH Terms] OR "work"[All Fields]

Cancer: "cancer's"[All Fields] OR "cancerated"[All Fields] OR "canceration"[All Fields] OR "cancerization"[All Fields] OR "cancerized"[All Fields] OR "cancerous"[All Fields] OR "neoplasms"[MeSH Terms] OR "neoplasms"[All Fields] OR "cancer"[All Fields] OR "cancers"[All Fields]



**Supplementary Figure 1.** The association between shift work and pancreatic cancer after including the Parent et al.<sup>[16]</sup> study (case-control study).