THE ASSOCIATION BETWEEN NIGHT WORK AND BREAST CANCER: AN UMBRELLA REVIEW OF SYSTEMATIC REVIEWS AND META-ANALYSES OF OBSERVATIONAL STUDIES

MASTER THESIS DEFENSE

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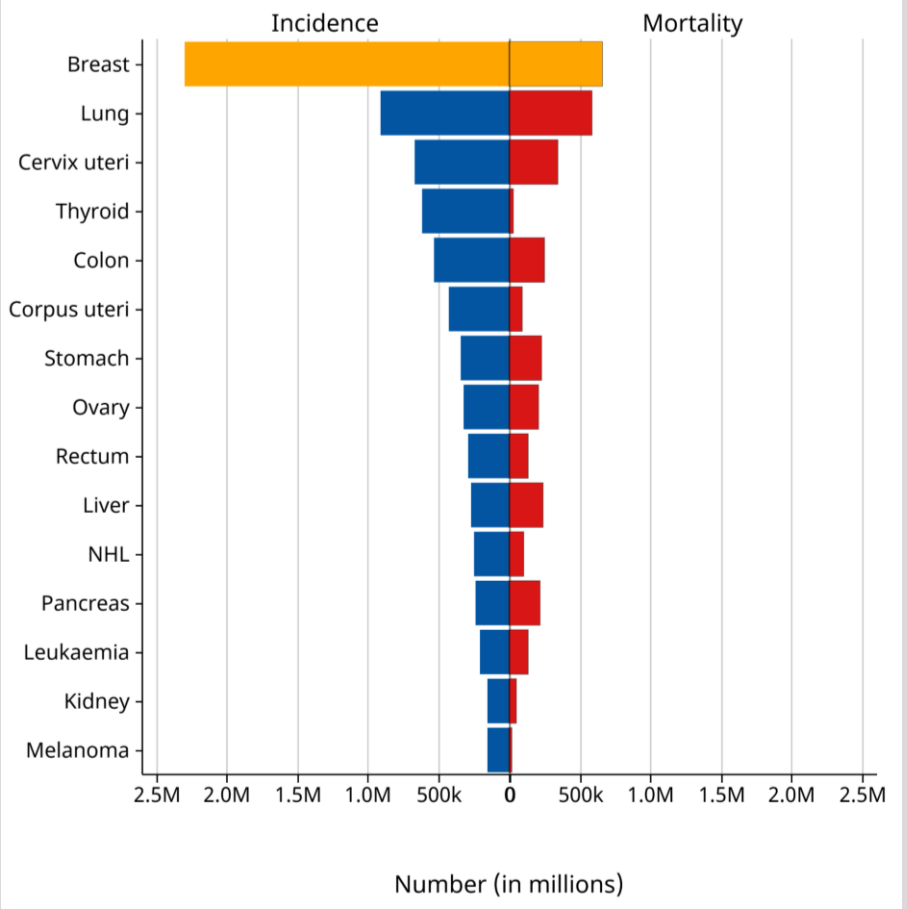
Plan of the presentation

- Background
- Methods
- Results
- Discussion
- Conclusion

Breast cancer worldwide

- Most frequently **diagnosed** cancer among women in 2022.
  - *2.2 million new cases*
- Leading cause of **cancer-related deaths** among women in 2022.
  - *Nearly 670’000 deaths*
- **By 2040**: 3 million new cases per year and 1 million deaths per years related to breast cancer.

Absolute numbers, Incidence and Mortality, Females, in 2022
World
(Top 15 cancer sites)



Cancer TODAY | IARC - https://gco.iarc.who.int/today
Data version : Globocan 2022 (version 1.1)

Night work

- Potential modifiable risk factor for breast cancer.
- Night work as «**probably carcinogenic**» (Group 2A) according to the International Agency for Research on Cancer (IARC) in 2007.
- **Definition**: at least 3 hours of work between 23:00 and 06:00.
- **Work sectors**: security, health and care work, transportation and warehousing.
- **17%** of working women were concerned by night work in 2021 in the 27 European Union countries.
- Several **biological mechanisms** (e.g. disrupted circadian rhythm) linking night work and breast cancer have been identified.

Objectives

→ *Meta-analyses and systematic reviews yield **contradictory** findings, and the evidence remains inconsistent.*

The umbrella review aimed to:

- **synthesize** the available evidence from **systematic reviews and meta-analyses** of observational studies on the relationship between night work and breast cancer in women.
- critically **assess** the methodological quality of these reviews.
- explore potential **explanations for discrepancies** in findings.
- **determine** whether night work is a **risk factor** for breast cancer.

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Methods

- Following Preferred Reporting Items for Systematic Reviews and Meta-Analyses (**PRISMA) guidelines.**
- **Systematic literature search** across PubMed, PsycINFO, Web of Science, and the Cochrane Library until 25 February 2024.
- Additional **manual searches** through screening reference lists and with the use of various artificial intelligence tools until February 2025.
- **Study selection** with predefined eligibility criteria.
- Structured **data extraction.**
- The **quality** and the risk of bias of the included reviews were **assessed** using the Critical Appraisal Tool from the Center for Evidence-Based Medicine (CEBM) and the Risk Of Bias In Systematic reviews (ROBIS) tool.

➢ *All steps mentioned above, except for the literature search, were performed by two independent authors, and any discrepancies were resolved by a third author.*

Eligibility criteria

Inclusion criteria:

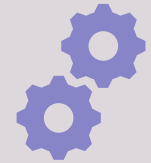
- **Systematic reviews or meta-analyses** of observational studies corresponding to the **PECO**
- All breast cancer **types** and **stages**
- No restrictions on the **publication period**

Exclusion criteria:

- Other **language** than English, French, Dutch, German, Albanian, or Italian
- **Retracted** articles
- No **access** to full texts
- **Umbrella** reviews
- Focusing exclusively on **flight attendants**

Population	Working aged women
Exposure	Night work
Comparator	No night work
Outcome	Incidence of breast cancer

Methods (2)



- Results from the included reviews were synthetized **narratively**.
- Several **exposure categories** according to the **IARC framework**:
  - *Overall night work (and ever versus never exposure)*
  - *Duration of night work*
  - *Cumulative exposure (with increasing number of years)*
  - *Cumulative exposure (with increasing number of night shifts)*
  - *Intensity*
  - *Shift system*
  - *Age at onset of night work*
- **Heterogeneity**, **study designs**, and **quality level** according to the ROBIS were considered.

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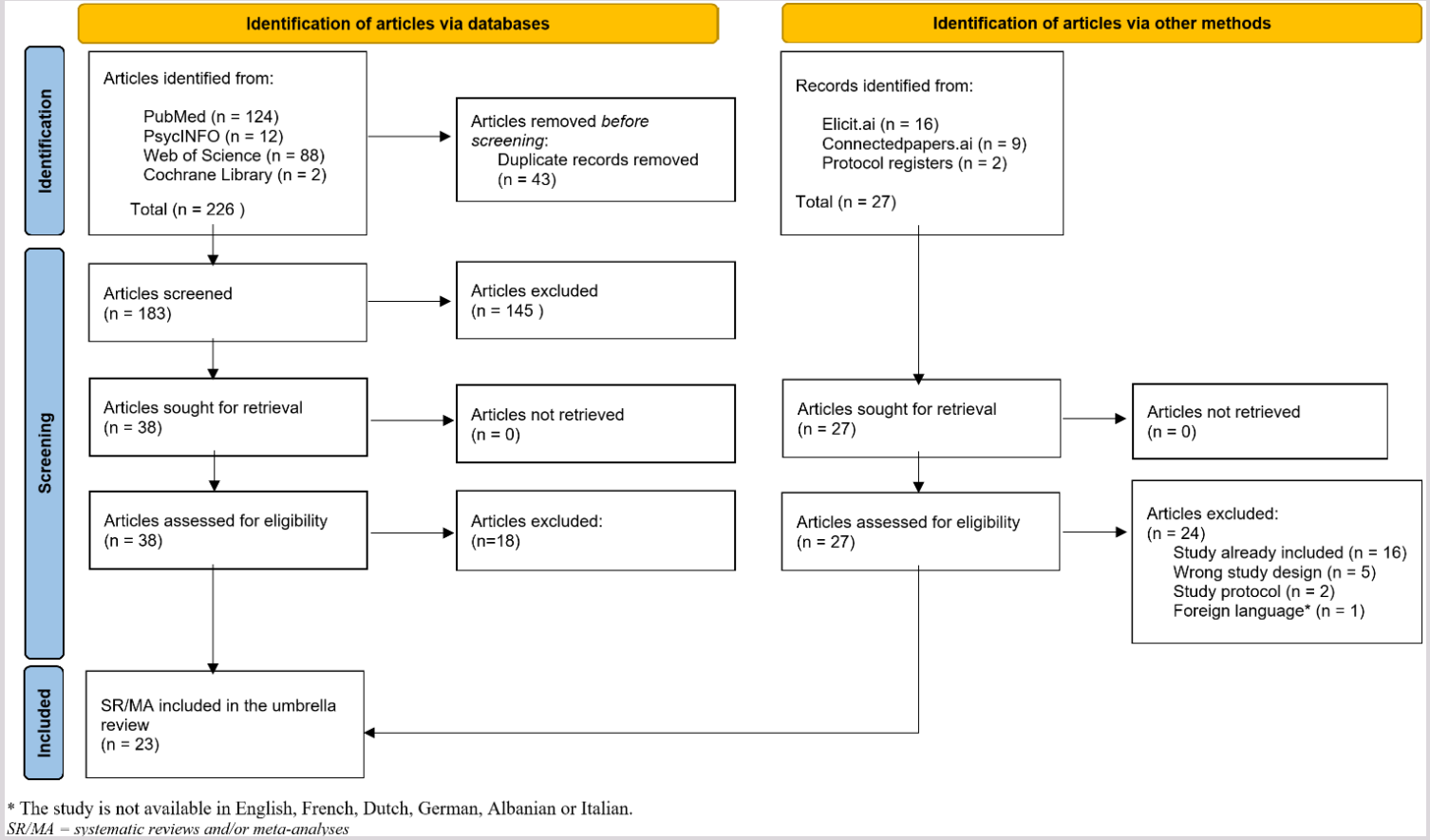
Search results

- **23** systematic reviews and meta-analyses were included.



Review characteristics

- **Six** qualitative systematic reviews and **seventeen** systematic reviews with meta-analyses.
- Published between **2005 and 2024.**
- A total of **72** primary studies.
- Several **work sectors:** nurses (N = 21), female military employees (N = 12), textile factory workers (N = 12), radio and telegraph operators (N = 9), flight attendants (N = 5), electromagnetic field workers (N = 1), and other unspecified (N = 22).
- Quality assessment :
  - *CEBM assessment* : ***high quality N = 6***
  - *ROBIS assessment* : ***high quality N = 4***
    - all reviews rated as high quality by ROBIS were also classified as high quality according to the CEBM evaluation.

Findings

- Potential **increase in risk** found in:
  - **Rotating** night shift schedules *(versus fixed schedules)*
  - **Flight attendants** *(versus other work sectors)*
  - **Pre-perimenopausal** breast cancer after more than **fifteen** years of night work *(versus postmenopausal)*
- **No convincing increase in risk** found in:
  - ***Overall effect :*** No increase in risk in cohort studies, heterogeneity.
  - ***Duration:*** Inconsistencies across study designs, heterogeneity, no consistent increase in risk found in high quality reviews.
  - ***Cumulative exposure:*** Inconsistencies across study designs, limited number of reviews.
  - ***Intensity:*** Inconsistencies across study designs, heterogeneity, limited number of reviews, high risk of bias in reviews.
  - ***Age at onset of night work:*** A meta-analysis reported no association between age at initiation and breast cancer risk.

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Summary of the findings

- **Potential increase in risk** found for**:**
  - Rotating night shift schedules
  - Flight attendants
  - Pre-perimenopausal breast cancer after more than fifteen years of night work

- **No convincing evidence** found in several exposure categories:
  - Overall effect
  - Duration
  - Cumulative exposure
  - Intensity
  - Age at onset of night work

Discussion

Rotating night shift schedules

Our findings show that **rotating** schedules **are potentially associated with higher increase in risk** than fixed schedules.

- **Not much literature** on the differential impact of fixed versus rotating schedules on breast cancer risk.
- Literature shows **no** difference in **sleep** quality or length between fixed and rotating schedules → sleep disruption doesn't account for the observed difference in breast cancer risk between the schedule types.

➢ Need of further **investigation.**

Discussion

Flight attendants

Flight attendants working on long-haul or overnight flights have a significantly higher increase in risk compared to women in other work sectors.

- **But** reviews focusing exclusively on flight attendants were **excluded**.
  - ***five*** meta-analyses identified during our search were not included in our main analysis
- **Unmeasured confounding factors,** such as cosmic radiation exposure and chronic jet lag, may have influenced the results.

- ➢ Needs to be interpreted with caution.
- ➢ Future studies and reviews specifically designed to evaluate this work sector, with careful assessment of confounding factors, are needed to clarify the nature of this association.

Discussion

Menopausal status

An exposure of **more than 15 years** of night work appears to be associated with an increased risk of **pre/perimenopausal breast cancer,** but not in postmenopausal breast cancer.

- **Biological mechanisms** :
  - *Postmenopausal women naturally produce lower **levels of oestrogen.***
  - ***Melatonin levels** and the **sensitivity of MT1 receptors** naturally decline with age.*
  - ***Specific life stages**, including prenatal development, puberty, pregnancy, and the menopausal transition, as **windows of susceptibility** for breast cancer.*
- Night-time exposure to artificial light was associated with an increased risk of breast cancer among premenopausal women in **previous meta-analyses**.

Discussion

Inconsistencies in the evidence

1. **Variation of the exposure characterization**
   - *Lack of standardized **definition** for night work.*
   - *Variation in the **classification** of shift types and in the thresholds used to define long-term exposure.*
   - *Lack of primary studies and reviews investigating shift domains according to the **IARC framework.***
2. **Methodological limitation in primary studies**
   - *Self-reported night work exposure.*
3. **Differing results depending on the study design**
   - *Statistically significance in the meta-analyses of **case-control studies**, but not in those of cohort studies and nested case-control studies → **Risk** of selection bias, recall bias in case-control studies; and **risk** of attrition bias in cohort studies.*
   - *A genuine effect should be observable **across** study designs.*
   - *Observed association in case-control studies are **insufficient** to establish a causal association.*
   - ***Imprecision** of analyses combining all study designs, these results were not sufficient to draw definitive conclusions.*

Discussion

Strengths and limitations

- **Up-to-date qualitative summary of all meta-analyses and systematic reviews published up to July 2024**
- Systematic and reproducible literature search
- Broad inclusion criteria
  - *no restrictions to specific work sectors [except for the reviews focusing exclusively on flight attendants]*
  - *or types of breast cancer*
  - *no date limitations*
  - *wide range of languages*
- PRISMA guidelines
- At least **two independent reviewers** and pilot phases
- **Quality and risk of bias assessment** by two senior authors, using two distinct tools
- Many subcategories of shift domains
- Stratification by work sector, menopausal status, and review quality
- Large number of meta-analyses and systematic reviews on the association between night work and female breast cancer risk

- **No extraction of data from primary studies**
- No adjustment for specific confounding factors
- No quantitative analysis
- **No extraction** of the presence of publication bias in reviews, of the number of primary studies contributing to each result, and of the methods of exposure assessment
- **Various sources of heterogeneity**
  - *Definitions of night work not explicit and variable*
  - *Inconsistent definition and investigation of shift domains in the included reviews*
  - *Imprecision of reported overall effect*
  - *Different exposure assessment methods in the primary studies (e.g., self-report versus objective measures)*
- Combination of all types of breast cancer
- No explicit statement that the focus was on women in seven reviews
- Exclusion of languages *(likely minimal impact)*

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Conclusion

- **Limited evidence** from cohort studies and high-quality reviews, and high heterogeneity across most findings
- **No establishment** of a causal relationship between the **duration, intensity or cumulative exposure** to night work and breast cancer risk
- **Rotating night shift schedules** also appear to be associated with an increased risk
- Night work exposure over 15 years or more may contribute to an increased risk of **pre- and perimenopausal breast cancer**
- **Flight attendants** may face a higher risk of breast cancer compared to women in other work sectors
  - *But this link needs to be confirmed through a dedicated (umbrella) review focused specifically on this subgroup, as we excluded such targeted reviews from our analysis*.
- The evidence remains **uncertain**, and further prospective studies and high-quality meta-analyses that examine night work with detailed exposure assessment are needed to generate more reliable and conclusive evidence

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Thank you for your attention.

QUESTIONS ?

Supplementary

Mechanisms linking night work and breast cancer

- Disruption of circadian rhythm
  - *Cell cycle*
  - *DNA repair*
  - *Immune function*
  - *Melatonin level*

- Uncontrolled cell growth
- Resistance to cell death
- Immune evasion

- Decreased melatonin level

- Genomic instability
- Tumor-promoting inflammation
- Angiogenesis
- Less anti-growth signals
- Less apoptosis
- More development of metastases
- Less attenuation of oestrogen's oncogenic effects

- Unhealthy lifestyles (poor diet, sedentary behavior, smoke)

Quality assessment

- **CEBM assessment** : **high quality N = 6**; moderate quality N = 3 ; low quality N = 14
- **ROBIS assessment** : **high quality N = 4**; low quality N = 19
  - *all reviews rated as high quality by ROBIS were also classified as high quality according to the CEBM evaluation*

First author	ROBIS*	CEBM score
Megdal	HIGH	2
Erren	HIGH	2
Kolstad	HIGH	-1
Wang	HIGH	0
Jia	HIGH	2
Ijaz	LOW	4
Kamdar	LOW	4
He	HIGH	2
Benabu	HIGH	-1
Lin	HIGH	4
Nikpour	HIGH	1
Travis	HIGH	1
McElvenny	HIGH	-2
Salamanca-Fernández	HIGH	2
Liu	HIGH	3
Dun	HIGH	2
Fagundo-Rivera	HIGH	2
Schwarz	LOW	4
Van	HIGH	3
Manouchehri	LOW	4
Wei	HIGH	2
Hong	HIGH	3
Moon	HIGH	5

**High or low risk of bias*