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Introduction to Research Proposal on Night Shift Work as a Probable Cause of Breast Cancer

Evidence-based medicine (EBM) and mechanistic reasoning are two approaches within medicine that are used to establish causal claims (Wilde, 2023). Causal claims refer to statements asserting that one factor causes another, for example, that smoking causes lung cancer. Evidence-based medicine integrates information from three key domains: the best available research evidence, clinical expertise, and patient preferences (Sackett et al., 1996). Within traditional EBM hierarchies, randomised controlled trials and systematic reviews of these trials are considered the highest level of evidence (Vatkar et al., 2025).

Mechanistic reasoning, in contrast, focuses on understanding the underlying biological mechanisms involved in disease processes or medical interventions (Park, Steel and Maine, 2023). This includes the study of physiology and pathophysiology, and how alterations in normal biological processes may contribute to disease development or influence the effectiveness of an intervention. Historically, evidence-based medicine and mechanistic reasoning have been treated as largely separate approaches when assessing causal claims in medicine (Marcum, 2011).

More recently, the EBM+ framework has emerged as a method that integrates both evidence-based medicine and mechanistic reasoning to support more reliable causal inference (Clarke et al., 2013). By combining epidemiological evidence with biological plausibility, EBM+ aims to overcome some of the limitations associated with relying on a single type of evidence.

The International Agency for Research on Cancer (IARC), part of the World Health Organisation, has classified night shift work as probably carcinogenic to humans (Working and For, 2021). This classification is based on evidence from observational studies alongside proposed biological mechanisms, while also acknowledging the presence of confounding factors.

Observational studies have historically underpinned early EBM methods, primarily through cohort and case–control studies (Sackett, 1998). However, relying solely on observational evidence might not be enough to determine causality. In cancer research, cohort studies with long follow-up periods can face increased risks of selection bias and attrition, and accuracy in exposure assessment may be compromised by recall bias or misclassification errors, which can distort results (IARC, 1980). While case–control studies are useful for investigating rare cancers, they are limited by biases in selecting cases and controls, as well as confounding factors unrelated to the main exposure, potentially skewing the observed associations (Wilde, 2021). Additionally, mechanistic reasoning, though it can elucidate possible biological pathways for cancer causes, does not necessarily prove causation. Even if a plausible mechanism exists, other factors or compensatory processes might counteract its effect, meaning the exposure might

not truly increase cancer risk in humans. For example, melatonin suppression due to night shift work being a proposed mechanism that links shift work to cancer risk, might be mitigated by counter regulatory physiological reactions.

Cancer is a complex, multifactorial disease that often develops following long-standing environmental or genetic exposures and has multiple causal pathways. As such, an EBM+ approach, which integrates epidemiological data with mechanistic and biological reasoning, is particularly suited to investigating potential carcinogenic exposures. This research proposal explores night shift work as a potential carcinogenic exposure by outlining a research question, methodology, methods, an analysis plan, and a critical appraisal of a relevant published study. It also compares the EBM+ approach with the review conducted by IARC.

Search strategy

The PICO framework was used to develop a search strategy. The population comprised adult night-shift workers, the exposure was night-shift work, the comparison was non-night-shift workers, and the outcome was breast cancer. This was then used to examine the association between nightshift work and breast cancers. For the search terms, synonyms of night-shift work were combined with a list of outcomes, as listed in Table 1. The keywords were combined with MeSH terminology using Boolean operators. Within concepts, OR was used, and between concepts, AND was used. The search databases used were PubMed and the Cochrane Library, which comprehensively cover biomedical, epidemiological and occupational factors.

The inclusion criteria encompassed studies of adult human populations, relevant animal studies and both quantitative and qualitative evidence, examined exposure to night-shift work, and reported outcomes for breast or prostate cancer, published in English from 2000 to 2025. Studies were excluded if they were reviews, editorials, opinion pieces, animal research, or lacked a clearly defined nightshift work exposure. Thus, the first hits in PubMed were 51 results and 11 on Cochrane.

Exposure terminology	Outcome Terminology
Night shift	Breast cancer
Rotating shift	Breast Neoplasm
Shift work	
Circadian disruption	
Shift worker	

Table 1

Critical Appraisal

This prospective cohort study addresses the clearly focused issue of examining whether there is a causal link between night shift work and breast cancer in the female population. The study uses a large population-based cohort of female participants from the Swedish Twin Register aged 41–60 who were included in this study. The exposure was years of shift work, and the outcome was breast cancer.

To assess for bias and methodological quality the study was appraised using the CASP cohort study checklist.

Due to objective data being used from the Swedish Cancer and National Health Registry, this reduces recall bias; however, there is a lack of exposure intensity and frequency being measured. The large population used from the Swedish registry increases representativeness while also reducing selection bias. However, there is limited occupational diversity based on the registers used. There is information bias regarding the exposure as it was self-reported data, in which the idea of night work was subjective, as it did not clarify whether late afternoon or early evening counted as night work. This is also a form of misclassification bias, as workers may interpret night work differently.

The outcomes gathered were highly reliable due to the cancer diagnosis being identified from the national cancer register and death register, increasing diagnostic accuracy and therefore reducing misclassification. This means the study had reduced information bias.

Confounding variables occur when there is a third variable that is associated with both the exposure and the outcome. This study accounted for many of these variables such as age, smoking, and occupational and reproductive factors; however, due to the loss of more than 50% of data on alcohol, they excluded it as a confounding variable but found that despite the loss of that data their results were still similar to current published data. Hence, the study accounted for confounder adjustment.

The study was highly reliable as it accurately estimates the association between exposure and outcome, although potential bias or confounding variables cannot be entirely excluded, and the external validity is low in terms of generalisability to other countries, men, and individuals of different occupations. The increased timeframe of the longitudinal follow-up aids in improving outcome detection and study reliability.

The results of the study do not show strong evidence of a significant association between night shift work and breast cancer in women, but some association was observed in those subgroups with long-term exposure (>20 years).

Overall, the study demonstrated moderate-to-high methodological rigour in the systematic approach to research used. It had the strength of a large sample size but limitations in generalisability, with the findings being less applicable outside of Sweden. Of the subgroups addressed, the confidence interval was narrow in some cases, indicating higher precision, whereas others had wider confidence intervals indicating lower precision.

Background Literature

Breast cancer is the most common cancer worldwide. The World Health Organization (WHO) reported that there were 2.3 million new breast cancer diagnoses in 2022 and 670,000 deaths globally (WHO, 2025). To address the growing body of evidence related to breast cancer epidemiology, the International

Agency for Research on Cancer (IARC) re-classified night shift work in which the body's circadian rhythms are disrupted as a probable carcinogen (Group 2A) which warrants further research into possible cause-and-effect relationships with breast cancer.

Establishing causality is crucial for a range of purposes, including disease prevention, occupational health policymaking, surveillance, and public health recommendations. Assessing whether an association between a risk factor and a disease is causal is a complex exercise that inevitably requires consideration of possible confounding factors that may influence disease aetiology independently of the risk factor of interest. In general, evidence-based medicine plus (EBM+) methods provide a framework to combine epidemiological evidence on the association of a risk factor with an outcome condition with mechanistic considerations thereby providing a comprehensive assessment of causality of the association.

The association between breast cancer and night shift work has been extensively investigated in the literature. One of the earliest and most influential studies was conducted by Eva S. Schernhammer and colleagues in the Nurses' Health Study, a prospective cohort study. The study assessed whether long-term rotating night shift work was associated with breast cancer risk. The study spanned a 10-year period from 1988 to 1998. Women were categorised into three groups based on their duration of rotating night shift exposure to breast cancer: never exposed, 1–14 years of exposure, and 15–29 years of exposure. The study found that women with 1–14 years of night shift work had a moderate increase in breast cancer risk, with an even greater increase seen in women with 15–29 years of exposure. Women with 30 years or more of rotating night shift work had about a 36% increased risk of breast cancer compared with women with no night shift work exposure. Exposure to 1–14 years of rotating night shift work was also associated with an increased risk of breast cancer in premenopausal women of about 23%.

The analysis controlled for several potential confounding variables such as age, age at menarche, parity, age at first birth, height, weight, menopausal status, family history of breast cancer and personal history of benign breast disease or breast cancer. Control for diet and alcohol was also introduced later in the study. However, several potentially important uncontrolled sources of variation include hormone levels, long term stress and other aspects of shiftwork and lifestyle.

A Swedish cohort study by Torbjörn Åkerstedt and colleagues (2015) investigated the association between night shift work and breast cancer risk in a large occupational cohort in Sweden. They found that only long-term night shift work over 20 years was associated with breast cancer. Shorter periods of night shift work did not show a statistically significant association. This suggests that duration of exposure to night shift work may be an important factor, and that cumulative circadian disruption can contribute to carcinogenesis.

There are several biological mechanisms that may underpin any association between breast cancer and shift work. Firstly, the body's master clock is situated in the Suprachiasmatic nucleus (SCN) within the hypothalamus. The role of the SCN is

to synchronise our physiological processes with a 24-hour circadian rhythm and involves hormone release and cell repair (Blakeman et al., 2016). The main control on our circadian rhythms is light. Light is detected at the retina and sent on to the SCN (Lewy et al., 1980). It has been proposed that light exposure from artificial sources in the evening (such as working the night shift), can disrupt the circadian rhythms and in particular decrease melatonin secretion from the pineal gland.

Melatonin is presumed to have an onco-static effect through regulating the tumour suppressor gene p53 (Lane, 1994). It is possible that decreased melatonin levels can lead to decreased tumour suppressor activity and a corresponding higher risk of cancer development. In addition, decreased melatonin secretion can lead to increased levels of reproductive hormones in the blood which can stimulate the proliferation of hormone dependent breast tissue. Other studies suggest that clock genes are expressed in breast epithelial cells, and that disturbances in circadian functions can affect cell cycle stability and thereby lead to cancer development. Melatonin has also been shown to act anti-mitotic in some studies, thereby limiting excessive cell division (Baldwin and Barrett, 1998).

Despite these observations the evidence base remains inconsistent. While several epidemiological studies suggest that breast cancer risk may be increased following long term night shift work, the evidence for short term exposure is less convincing. A possible reason for this inconsistency is that the definitions of night shift work used in the various studies are not universally standardised. As a result, the way exposure to night shift work is characterised can vary considerably between studies, and it is likely that the risk of developing breast cancer following night shift work may vary depending on the nature of the working environment, the characteristics of the study population, and the duration of follow-up.

Another limitation of current evidence is that much of the mechanistic evidence for circadian disruption and cancer is derived from animal studies, particularly rodents, which do not necessarily reflect human biology. Another concern is that there is considerable heterogeneity in how potential confounding factors (such as stress, hormones and behaviour) are controlled across different studies.

More research is needed to investigate the relationship between night shift work and breast cancer. Work to define and characterise ‘shift work’ should be undertaken, along with more rigorous control of potential confounding variables, and convergence of epidemiological evidence with mechanistic evidence is recommended. Ultimately, such an integrated approach may provide greater clarity on whether night shift work has a causal role in breast cancer aetiology.

Research Question

A possible link between night shift work and breast cancer has been suggested by epidemiological studies. The underlying mechanisms might be related to Circadian rhythm disruption and melatonin suppression, leading to increased carcinogenesis risk. Although several epidemiological studies have been published, they are however conflicting. Therefore, it is uncertain whether there is a true association

between night shift work and breast cancer risk. The purpose of this study was to investigate whether long term night shift work is a risk factor for breast cancer.

Research Question:

Adult women (P) working long-term night shifts (I) have a higher risk of developing breast cancer (O) than those working during the day (C) over time (T)?

Methodology

The research endeavours to follow the post-positivist research paradigm. This research orientation recognises an objective reality but acknowledges that scientific knowledge can only approximate this reality as achieved through systematic observation and analysis. In terms of the principles of epidemiology this research orientation acknowledges that it is possible for associations to exist between an exposure and an outcome but that they may be distorted by factors such as bias, confounding and study design. Thus, conclusions are drawn with caution and are guided by the quality and consistency of the evidence.

The epistemological position underpinning this study is primarily empirical, relying on measurable data derived from epidemiological studies investigating occupational exposures and breast cancer risk. However, the research also incorporates mechanistic reasoning, recognising that associations are strengthened when supported by plausible biological pathways. In the case of night shift work, mechanisms such as circadian rhythm disruption, melatonin suppression, and hormonal dysregulation have been proposed as potential contributors to carcinogenesis.

This study looks at how working night shifts might be linked to breast cancer by checking what another research has already found. To do this, it uses a method called a structured literature review, which is a way of finding and combining all the relevant studies on the topic. This approach helps make sure the process is clear and can be repeated, which reduces the chance of choosing studies unfairly and makes the conclusions more reliable.

Since it's not possible to do random controlled trials on things like shift work, researchers must rely on other types of studies. These include cohort and case-control studies, which let them look at how working night shifts for a long time might be connected to getting certain diseases later. They can use these studies to see if there's a link between working at night and health problems.

To ensure the reliability of the included evidence, the methodological quality of studies will be critically appraised using established tools such as the CASP Checklist for observational studies. This appraisal will allow the strengths, limitations, and potential sources of bias within individual studies to be systematically assessed and considered during the synthesis of findings.

Methods

This research will look at how working night shifts might be linked to breast cancer. We'll use a systematic approach to review what's already been studied and follow established guidelines to make sure our findings are reliable. Our goal is to gather and analyse all the relevant information from past research, including both observational studies and studies that look at the underlying mechanisms, to see if we can find any connection between night shift work and breast cancer risk.

Data Sources

A comprehensive search of electronic databases will be conducted to identify relevant literature. The primary databases will include PubMed/MEDLINE, Embase, Scopus, and Web of Science. Additional grey literature may be identified through Google Scholar and reference list screening of relevant studies. Searches will include literature published from 2000 onwards to capture contemporary research reflecting modern occupational patterns.

Search strategies will combine key terms and MeSH headings related to the exposure and outcome, including: “night shift work”, “shift work”, “circadian disruption”, “melatonin suppression”, and “breast cancer risk”. Boolean operators (AND/OR) will be used to refine searches.

Studies will be eligible for inclusion if they:

- Investigate night shift or rotating shift work as the exposure
- Examine breast cancer incidence or risk as the outcome
- Are observational studies (cohort, case-control, or cross-sectional)
- Are published in peer-reviewed journals
- Are written in English

Studies will be excluded if they:

- Are animal or laboratory-only studies without human epidemiological context
- Focus on other cancer types without reporting breast cancer outcomes
- Are editorials, commentaries, or narrative reviews
- Provide insufficient methodological detail

Screening Process

All identified records will be imported into a reference management software (e.g., EndNote or Zotero) and duplicates removed. Screening will occur in two stages:

- Title and abstract screening to identify potentially relevant studies.
- Full-text screening against the inclusion and exclusion criteria.

This process will ensure that only relevant studies addressing the research question are included in the final analysis.

PRISMA Framework

To make sure our review is thorough and easy to follow, we'll use the PRISMA guidelines. This means we'll keep track of all the studies we find, look at, and decide to use or not use. We'll use a special diagram to show how many studies we start with, how many we look at closely, how many we don't use, and how many we include in our review. This way, everyone can see what we did and how we did it.

Data Extraction

To get the information we need, we'll create a special table to collect data from each study in a systematic way. This table will help us gather key details, including:

- Study design and setting
- Sample size and population characteristics
- Definition and duration of shift work exposure
- Outcome measures relating to breast cancer incidence
- Key findings and reported effect sizes
- Potential confounders considered (e.g., age, reproductive history, lifestyle factors)

This approach will enable us to compare results from different studies in a consistent way, making it easier to combine the findings and get a clearer picture of what the evidence is telling us.

Analysis Plan

The results of the studies that are part of this research will be combined using a method that involves summarizing the main ideas and themes. This approach is suitable for the type of data being used, which is varied and not easily comparable. The information from the studies that looks at the relationship between working night shifts, and the risk of breast cancer will be organized into main topics, such as how long someone works at night, the type of job they have, and how much their risk of breast cancer increases.

In addition to epidemiological findings, the review will integrate evidence relating to biological plausibility, particularly mechanisms involving circadian rhythm disruption, melatonin suppression, and hormonal dysregulation.

To figure out if what we're seeing is causing something, we need to look at how strong the evidence is. We'll use some of the Bradford Hill principles to do this, like checking if the results are consistent, if things are happening in the right order, if it makes sense biologically, and if there's a clear relationship between the dose and the response.

This approach will provide a fair and balanced look at both the evidence from epidemiology and the underlying mechanisms that support the suggested link, allowing for a more comprehensive understanding of the relationship.

Ethics

This research is based on existing studies, so it's not necessary to get approval from the NHS Research Ethics Committee. According to the UK Health Research Authority, studies that only look at previously published work don't need this approval. The project will analyse and combine information from earlier research, rather than collecting new data from people. This approach is allowed because it doesn't involve directly working with human participants, which is what the NHS Research Ethics Committee typically reviews.

Despite the absence of direct participant involvement, ethical research practices remain essential. A key consideration is data integrity, ensuring that findings from included studies are accurately represented and interpreted. Selective reporting or misrepresentation of results will be avoided by adhering to systematic review principles and transparently documenting the study selection and analysis process.

Research transparency will also be prioritised. The methodology will be clearly described, including search strategies, inclusion criteria, and screening processes. The use of the PRISMA framework will further support transparency by documenting how studies were identified and selected.

Potential sources of bias will be acknowledged and critically evaluated. Publication bias may occur if studies with statistically significant findings are more likely to be published. Additionally, observational studies examining occupational exposure are vulnerable to confounding factors such as lifestyle behaviours, socioeconomic status, and reproductive history, which may influence breast cancer risk.

This study will carefully look at how well the included studies were done and think about their limitations when trying to understand all the evidence. To be fair and honest, the study will make sure to follow strict methods and be open about what it does, so it can give a balanced view of what we currently know about working night shifts and the risk of breast cancer.

Dissemination

This study's results will be shared with others through a few different academic channels. First, there will be a presentation at the Year 4 Individual Research Project, where the findings will be discussed with supervisors and fellow students. It's also possible that the study could be presented at a student research conference or an undergraduate research symposium, which would allow the results to be shared with a larger group of people in the academic community. This would be a great way to get the findings out to more people and get feedback from others in the field. By sharing the results in these ways, the study can reach a wider audience and contribute to the ongoing discussion in the academic community.

Disseminating this research is important given the potential public health and occupational health implications of night shift work. Improving awareness of the evidence surrounding circadian disruption and cancer risk may contribute to future discussions on workplace policy, employee wellbeing, and preventative health strategies.

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