

## Risk of breast cancer among female shift workers (systematic review)

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### Abstract

**Background:** Shift work may increase the risk of breast cancer by decreasing melatonin production. This phenomenon by affecting pituitary gland and sexual hormonal secretion may increase the risk of breast cancer. The aim of this review study was to evaluate the results of studies for determining the relationship between shift work and breast cancer.

**Methods:** Data collection was done through worksheets appropriate to research objectives and searching among databases, including Medline, Google scholar and Scopus. Search keywords included shift work, night work and breast cancer. Studies were eligible for inclusion if they were observational, case-control or cohort studies that compared female shift workers with day workers. Animal studies, the studies that only examined mortality and benign breast disease, and works related breast cancer without focusing on shiftwork were excluded. Finally, a total of 16 studies consisted of 5 cohorts and 11 case controls were assessed.

**Results:** Among the prospective cohort studies, two studies reported an increased risk of breast cancer in association with shift work, but the rest did not find any relationship. Four of 11 case-control studies, indicated relation between shift work and breast cancer, but the remaining 7 studies did not report such finding. However 4 of 7 studies demonstrated that possibility of breast cancer will increase with increased number of night work per month and years of night work.

**Conclusion:** We concluded that shift work is a certain threat for females' health, and there may be the increased risk of breast cancer associated with long term night shift work.

**Keywords:** Females, Shift work, Night work, Breast cancer.

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The shift work that is considered as an unconventional paradigm and out of official hours (arbitrarily between 6 pm to 7 am), is a pattern which, although in the past centuries some working group such as bakers and lodging operators have practiced it (1, 2), but in recent decades, especially after the invention of the light bulb, has had a significant expansion as far as the proportion of shift workers in industrialized countries is allocated between 15 and 30 percent of the total workforce (3-6). It is expected that its real hit is even more in developing countries for reasons such as lack of proper discipline and working irregular hours (3,7).

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In addition to those, due to the need for technological limitations or economic pressures, have to work continuously day and night, many manufacturing and service sectors also rely on shift work. Shifts in the medical care field are naturally circadian, and doctors and nurses often are obliged to provide services based on a 24-hour system (8). Most of health care providers in all countries are female shift worker (rotating, evening and night) (9). Use of artificial light during night shifts is accompanied by disorders in the body's biological clock (circadian rhythm), and it is followed by disorders in the secretion of melatonin, and reduction of its production (10). This hormone is naturally made in the body by the pineal gland in the brain, which increases in the dark during the night and reversely reduces during daylight. The secretion of melatonin helps to regulate sleep-wake cycle (11-12). The role of this hormone, in addition to the above, is in some other physiological activities such as antioxidant effects and scavenging of free radicals, preventing premature death of cells, enhancing the immune system, and preventing premature aging and also plays an effective role in the treatment of depression, and dealing with HIV infection and suppressing the growth of cancer cells (13-14). Shift work is a kind of working pattern in a large group of people who have abnormalities in biological rhythms, sleep-wake cycle, and melatonin secretion; so, they are suffering from harmful effects, such as sleep disorders, fatigue, digestive disorders and heart disease (15-20). However, this working pattern is associated with a disruption in social activities and family life (11). Previous studies have shown that shift work and increased working hours have harmful effects on mental health, life satisfaction, a sense of happiness, a feeling of health and marital satisfaction (21-27). The pituitary gland is responsible for the production of sex hormones affects the circadian cycle, and naturally following the disturbance of the circadian cycle, causes irregularities in the production of sex hormones and the subsequent problems in the process of menstruation in women (28).

According to some researches, the night work (as a form of shift works) caused irregularities in hormone production, and this in turn leads to an increased risk of multifactorial cancers, especially hormone-dependent cancers such as breast cancer, endometrial and ovarian cancers (29-37). Such documentation has led the International Agency for Research on Cancer- IARC classified shift work as a probable human

cancer hazard in 2007 (38). Findings in human studies indicate an association between breast cancer risk and the level of melatonin metabolites in the urine (39-40). Based on these findings, the urinary metabolite of melatonin in night-shift nurses was significantly less than their day shift counterparts (41). Breast cancer is the most common cancer in women, and considered as a leading cause of cancer death in women, also that only 20-40% causes of breast cancer are known and many causes are still unknown (42-44), and the conflicting results about the relationship between shift work and breast cancer have published (31-35), this study aims to review the published reports in the context of shift work and breast cancer risk.

## Methods

Data collection was done using work sheets appropriate for the purposes of scientific research and search was done through databases, including Medline, Google Scholar, and Scopus. To select the relevant articles, the keywords: shift work, night shifts and breast cancer were used. Quality assessment of studies (proper design, sample size, duration of follow-up, proper analysis and outcome) was performed by Critical Appraisal Skills Program (45), and middle and high quality studies were selected. Inclusion criteria for this review study were: a) comparison of samples among women working night shift and those who work day shift, also prospective cohort, case-control and retrospective studies, b) breast cancer pathology samples have been determined, c) Shifts in the studies should be defined at least based on one of the following concepts: the working shift system (shift rotation, fixed night shift, shift work with forward or backward turn), time shift during the year (starting and finishing time) and the shift work rate in a week or month.

Animal studies as well as the studies only looking at mortality and benign breast diseases, or the studies evaluating the relation of job without assessing shift work and night shift were excluded.

At first, 626 studies were found by searching shift work and breast cancer Key words, 192 of these studies were published; after examining the inclusion and exclusion criteria and quality assessment, at the end 16 studies were assessed (30-35, 46-55), 5 prospective cohort studies (31-32, 46-48), which had between 5 and 19 years of follow-up, and 11 case-control studies (30, 33-38, 49-55). Five studies were

about nurses and one study for telegraph and telephone operators; one study on female workers employed in textile factories, and one study on women in the military and 7 other studies on different jobs. Study participants were aged between 20 and 85 years (Tables 1 and 2). In most studies, the night shift was defined as jobs which had start and end times during the night. Data analysis tools for published articles were in a form of interviews, questionnaires or information recorded in the relevant centers. In all studies, samples are matched in terms of one or more variables with the risk factors for breast cancer such as age, age at menarche, age at birth of first child and using contraception drugs.

## Results

From 5 prospective cohort studies, the two studies reported an increased risk of breast cancer due to shift work (32, 46). In two recent studies, one study was conducted in the USA and the subject was followed for 3 years on nursing women (32), and another study by Knutsson et al. was done in Sweden for 12 years on women with different jobs (46). Three other Cohort studies found no association between the two variables (31, 47-48). The study of Schernhammer et al.

on American work shift nurses in periodic follow-up for 11 years, the risk was reported only after 20 years of night shift (31). Study of Schwartzbaum et al. in a prospective cohort study with follow-up for 19 years on the Swedish working men and women found no increased risk of prostate and colon cancer in men and also in women with breast cancer (48). Another study was conducted in China, with 5-year follow-up that reported no relation between shift work and breast cancer (47).

From 11 case-control studies, researchers in 4 studies reported that shift work is associated with the increased risk of breast cancer in women (30, 33, 49, 53). The results of Menegaux et al. study from France on women with different jobs indicated that breast cancer risk in female shift worker is more than the control group (13% vs 11%), and the risk was higher in women who had their first child before they start work and work experience more than 4.5 years (53). In contrast, in the other 7 studies, night shift was not mentioned as a risk factor for breast cancer; of course, among the 7 most recent studies, the results of four studies have shown that with the increased number of night shifts per month, as well as increased year of night work for women, there would be an increase in the risk of breast cancer (34-35, 52-54). Characteristics of studies presented in Tables 1 and 2.

**Table1: Characteristics of some studies regarding breast cancer risk among shift workers**

| Researcher               | Study Time | Place of Study | Data Collection             | Study Design       | Mean Age of the Sample | Job                           |
|--------------------------|------------|----------------|-----------------------------|--------------------|------------------------|-------------------------------|
| Davis, et al (30)        | 2001       | USA            | Interview                   | Case-Control       | 47                     | Different                     |
| Hansen (34)              | 2001       | Denmark        | File                        | Case-Control       | 42                     | Different                     |
| Hansen, et al (49)       | 2011       | Denmark        | Interview                   | Case-Control       | 70<                    | Nurse                         |
| Hansen, et al (50)       | 2012       | Denmark        | Questionnaire and Interview | Case-Control       | 70<                    | Military women                |
| Knutsson (46)            | 2012       | Sweden         | Questionnaire               | Prospective Cohort | 41                     | Different                     |
| Li, et al (51)           | 2011       | China          | Interview                   | Case-Control       | 48                     | Nurse                         |
| Lie, et al (35)          | 2006       | Norway         | Interview                   | Case-Control       | 56                     | Nurse                         |
| Lie, et al (52)          | 2011       | Norway         | Interview                   | Case-Control       | 54                     | Textile workers               |
| Menegaux, et al (53)     | 2011       | France         | Interview                   | Case-Control       | 49                     | Different                     |
| O'Leary, et al (54)      | 2006       | German         | Interview                   | Case-Control       | 55                     | Different                     |
| Pesch, et al (55)        | 2010       | USA            | Interview                   | Case-Control       | 56                     | Different                     |
| Pronk, et al (47)        | 2010       | China          | Interview                   | Prospective Cohort | 52                     | Different                     |
| Schernhammer, et al(32)  | 2001       | USA            | Questionnaire               | Prospective Cohort | 55                     | Nurse                         |
| Schernhammer, et al(31)  | 2006       | USA            | Questionnaire               | Prospective Cohort | 40                     | Nurse                         |
| Schwartzbaum, et al (48) | 2007       | Sweden         | File                        | Prospective Cohort | 57                     | Different                     |
| Tynes, et al (33)        | 1996       | Norway         | File                        | Case-Control       | 52                     | Telegraph and radio operators |

**Table 2: Statistical parameters in some studies regarding breast cancer risk among shift workers**

| Researcher               | Analysis Results |                 | The Number of Samples |                    |
|--------------------------|------------------|-----------------|-----------------------|--------------------|
| Davis, et al (30)        | OR: 1.14         | CI (1.01, 1.13) | Case: 768             | Control: 741       |
| Hansen (34)              | OR: 1.5          | CI (1.2, 1.7)   | Case: 6281            | Control: 6024      |
| Hansen, et al (49)       | OR: 2.9          | CI (1.1, 8.0)   | Case: 267             | Control: 1035      |
| Hansen, et al (50)       | OR: 2.3          | CI (1.1, 8.0)   | Case:132              | Control: 505       |
| Knutsson, et al (46)     | RR: 1.23         | CI (0.7,2.17)   | Expose: 549           | Non Exposed: 2511  |
| Li, et al (51)           | RR: 1.03         | CI (0.84,1.21)  | Case: 1709            | Control: 4780      |
| Lie, et al (35)          | OR: 2.21         | CI (1.10, 4.5)  | Case: 537             | Control: 2143      |
| Lie, et al (52)          | OR: 1.20         | CI (0.8, 1.6)   | Case: 699             | Control: 895       |
| Menegaux, et al (53)     | OR: 1.27         | CI (0.99-1.64)  | Case:1232             | Control: 1317      |
| O'Leary, et al (54)      | OR: 1.65         | CI (1.02, 2.69) | Case: 487             | Control: 509       |
| Pesch, et al (55)        | OR: 1.83         | CI (1.15, 2.93) | Case: 746             | Control: 793       |
| Pronk, et al (47)        | OR: 1.73         | CI (0.71, 4.22) | Exposed: 18234        | Non Exposed: 51236 |
| Schernhammer, et al (32) | RR: 0.9          | CI (0.7, 1.1)   | Exposed: 46801        | Non Exposed: 31761 |
| Schernhammer, et al (31) | RR: 1.79         | CI (1.06, 3.01) | Exposed: 78063        | Non Exposed: 35153 |
| Schwartzbaum, et al (48) | SIR: 0.94        | CI (0.74-1.18 ) | Exposed: 70           | Non Exposed: 274   |
| Tynes, et al (33)        | OR: 1.5          | CI (1.1, 2.5)   | Case: 50              | Control: 259       |

## Discussion

This review aimed to examine the association between shift work and breast cancer in women. Six of the 16 studies showed that with increased duration of shift work, especially after 20 years, or increased number of shifts per week or month, the risk of breast cancer increases in women (31, 34, 35, 46, 52, 54). In 5 studies conducted on nurses to assess breast cancer risk, 2 studies reported the increased risk of cancer with shift work (32, 49), and in 3 other studies, the increased risk was reported if the duration or length of work year increase (especially more than 5 years) (31, 35, 52). It seems that the long-term shift and reduced melatonin secretion have an important role in the incidence of this complication. Obviously, the more accurate judgment on this issue requires laboratory research and urinary melatonin metabolite changes review during the first year of employment as shift work up to the end. It is only then that it can be more carefully judged about the relationship between shift work and increased risk of breast cancer in shift workers.

According to current knowledge, the mechanisms involved in the apparent protective tumorigenesis of melatonin is attributed to roles such as a direct anti-proliferative effect, strengthening the immune system, preventing the creation of free radicals in the body and also the expression of P53 gene as breast tumor suppressor.

Complete inhibition or reduction of melatonin secretion in the body depends on factors such as long-term exposure to artificial light during the night shift, also its intensity and wavelength. Onset or growth of cancer cells in the body is associated with reduced levels of melatonin (50). Multiple and often consecutive shift work can disrupt the circadian rhythm and some associated biological functions such as sleep problems, while small number of shift work about one or two nights per week probably is not associated with the disorder and severe problem in circadian rhythm (52).

Therefore, it is recommended to adopt measures such as:

- Assign a smaller number of night shifts per week or month or in fewer years of working life,
- Run the shift program to rotate forward (morning, afternoon, evening),
- Choose shift work persons on a voluntary basis,
- Offer special pattern of shift work with fewer long hours at night (for example, 8 hours in the morning, 9 hours in the evening and 7 hours evening and night-time),
- Breast cancer screening for night shift workers with a history of more than 5 years

According to the findings, the risk of breast cancer in morning preference is more than an evening preference (50). Morning preference is a major inhibitor in harmony and consistent with the work shift and these individuals have more severe circadian rhythm disorder. Therefore, to reduce

the effects of shift work, it is essential to consider this characteristic of the individual.

The distinctive feature of this review article is to summarize researches on breast cancer in women who work day shift compared to those who work night shift. But in the last review studies, comparing cancer among shift work women with other women was done in a way that even non-working women were also entered and evaluated because of the inclusion criteria (30, 42). So it seems that the results may have less bias, and also better and more precise estimate of the risk of breast cancer in shift works is provided.

Breast cancer, with an incidence of about 22% is known as the most common cause of cancer deaths in Iranian women and compared to the developed countries, the average age of women suffering from this condition is a decade less than their counterparts (56). The online search on multiple scientific studies have shown that there is no research trying to study the relationship between shift work and breast cancer. Thus, since Iran is a developing country, and for reasons such as lack of proper organization and irregular work hours, there are higher hours of shift work in some businesses (3, 7) and also in some jobs, especially in health care services, due to lack of workforce, they face with the problem of overtime in shift workers (57), So more studies should perform in this regard.

In the end, the prospective cohort studies extensively in different regions and in different professions, especially medical staff that the vast majority of it is women are needed to obtain more precise results in order to judge more certain about the adverse consequences of shift work and apply preventive measures.

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