Night shift work and female cancers

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MPH project

Supervisor professor: Dr. Tim Takaro

By Farzaneh Mirzaaghaee

Introduction

As the world moves towards greater industrialization, shift work is becoming more common. Around 15% of US workers and more than 17% of European Union working populations are involved in shiftwork including night shift work (1),(2). Shiftwork in developing countries is expected to be higher for reasons such as lack of proper discipline and working irregular hours due to the lack of proper labor law (3).

The occupations that have the highest numbers of evening and night shift works are hotel, restaurant, health care, gas station and transport industries (2). For example, around one-third of European health-care workers works as shift workers (4). Also, according to the latest data of Carex Canada more than 250000 Canadian women work in health care and social assistance industries (5)

The 4th EU survey on working conditions showed that women are equally employed in shift work including night shift as men(4).

Night shift work can cause various health problems. In recent years the role of night shift work in different cancers has been discussed. Three important female cancers are breast, endometrial and ovarian cancers. Breast cancer is one of the major causes of morbidity and mortality among women representing about 23 percent of all female cancers and an important leading cause of death (6). Recognized risk factors for breast cancer include genetic mutations, family history of breast cancer, and some features of reproductive history, but lifestyle, environmental, or occupational causes of breast cancer are incompletely identified (7). Endometrial cancer is the most common gynecologic malignancy, causing about 700 deaths

annually in the US (8). Ovarian cancer is another important female cancer that caused more than 15,000 deaths in the US in 2012 (9).

The mechanisms of the effect of sleep habits on female cancers are complicated. One of the mechanisms hypothesized to be part of the relationship between night shift work and female cancers is the role of melatonin. Night shift through different mechanisms including exposure to light at night and short sleep duration, may cause the disturbance of circadian rhythm due to the reduction of the melatonin synthesis (10).

Melatonin, a hormone primarily produced by pineal gland is high at night and low during the day, induces sleep onset and maintenance, reduces sleep latency, improves sleep efficiency and increases the total sleep time (11). It also coordinates the circadian rhythm and acts as a neuroendocrine transducer of the light-dark cycle (12). Melatonin modulates the cell-cycle length through control of the p53/p21 pathway and also has antioxidant and antimiotic activity and facilitates the reduction of oxidative stress, it can be an oncostatic agent (13).

Night shift work can disrupt circadian rhythm, suppress melatonin secretion and result in sleep deprivation, all of which may increase the initiation, progression and growth of human tumors through cell cycling and apoptosis (14). On October 2007, the International Agency for Research on Cancer (IARC) classified shift work with circadian disruption as a group 2A carcinogen (probable human carcinogen) (2).

Night shift through exposure to light at night may decrease the melatonin production. Light at night eliminates the melatonin signal and its suppression of tumor linoleic acid uptake and metabolism to 13-hydroxyoctadecadienoic acid (15).

Also, as female night workers have exposure to light at night, their menstrual cycle lengths may be shortened which might increase the risk of breast cancer (16).

Moreover, melatonin suppression increases the gonadotrophins release leading to an elevation of estrogen levels, causing estrogen induced cancers such as breast, endometrial and ovarian cancers (17). Melatonin can block the alpha estrogen receptor ERα (but not ER β) (18). In addition, melatonin inhibits aromatases, the enzymes which control the conversion from androgenic precursors to estrogens causing lower synthesis of estrogens (19).

Also, Night shift work may result in the disruption of communication between the 'master clock' in the suprachiasmatic nuclei and peripheral molecular clocks, abnormal expression in clock genes and epigenetic change of circadian genes, all of which may have role in female carcinogenesis (20-22).

Finally, the seasonal relationship of melatonin and production of ovarian hormone has been suggested, so that a longer melatonin surge during the night in winter than in the summer (23).

As shift working is becoming more common among women and one of the effects of disruption of circadian rhythm is through different mechanisms including the effect of melatonin on estrogen level, in this review we have studied the effect of shift work on female cancers.

Objectives

This review aimed to identify evidence from different observational studies that could inform the hypothesis that night shift work is associated with an increase in the risk of female cancers.

Methods

Web search using appropriate keywords was done by using Medline, Scopus, Embase and CINAHL till June 2016. Searched Mesh terms used were: “Shift work” OR “night shift” OR “Sleep Disorders, Circadian Rhythm” AND “cancer” OR “neoplasm” OR “women cancer” OR “women neoplasm” OR “female cancer” OR “female neoplasm” OR “breast cancer” OR “breast neoplasm” OR “ovarian cancer” OR “ovarian neoplasm” OR “ovarian cancer” OR “ovarian neoplasm”. The publications that were found were critically reviewed, with particular concentration on their methodological quality and potential biases. Papers published before 2007, review articles, studies done on animals, case reports, non-English language studies, editorials studies and those that did not present hazard ratio (HR), odds ratio (OR), relative risk (RR), or standardized incidence ratio (SIR) estimates with 95 % confidence intervals (CI) were excluded.

Altogether 54 articles were found. They were all reviewed, of which 19 were uninformative on the hypothesis or published in a language other than English and did not meet eligibility criteria. Of the remaining 35 papers, 6 commentaries or hypothesis-generating reports and 15 reviews were not included in this article. Two letters to the editor not presenting original data were excluded. Finally, 12 studies were included in this review.

The quality of studies was assessed using the Newcastle Ottawa scale (NOS) (24). A study was judged in three sides: the selection of the study groups, the comparability of the groups, and the ascertainment of the exposure or outcome of interest. For the comparability between the groups, these variables were selected from previous studies (25): age, age at menarche, age at first birth, menopausal status, body mass index (BMI), education level, family history of cancer,

hormone use, parity, physical activity, number of child birth, alcohol and smoking. Checklist for quality assessment is shown in table 1. The full score was 7 stars, and high-quality studies were defined by a score of 4 stars or more.

Results

A total of twelve studies met our inclusion criteria. Their descriptions have been summarized in table 2. Among the twelve studies, statically significant results were found in six (four in breast cancer, one in endometrial and one in ovarian cancer).

Results of borderline significance were reported in three studies (two in breast cancer and one in ovarian cancer).

In three studies, the findings were not statically significant (all in breast cancer).

Three Studies were conducted in US, seven studies in Europe and two studies focused on women from Asia (China). The definition of night work varied across studies (Table 3). In most of the studies, night work was assessed by interview and questionnaire. Results from the assessment of study quality showed that 10 out of 12 studies achieved 4 stars or above, and were regarded as high-quality studies. For method of exposure measurement, none of studies used objective exposure assessment. The lowest prevalence of night shift work was observed in two of studies that showed no significant relationship between night shift work and cancer (Schwartzbaum et al. followed by Pesh et al.).

Breast cancer

Overall six case-control and three cohort studies about the relationship between night shift work and breast cancers have been included in this review. Three of the nine studies included, showed no relationship between night shift and breast cancer (Pronk et al., Schwartzbaum et al. and Pesh et al.).

Pronk et al. conducted a prospective cohort study of 73049 women aged 40-70 years old in 2010, of which 44% were classified as having ever night-shift working in their occupational history. Women were interviewed between 1996 and 2000 and were followed for 9 years. During the 9 year follow up, 717 new cases of breast cancers were diagnosed through Shanghai cancer Registry. The study showed no significant association between breast cancer and night shift work, neither in job-reported matrix (OR=1, 95% CI= 0.9, 1.2) nor in self-reported history of night-shift work (OR=0.9, 95% CI= 0.7, 1.1) (26).

Schwartzbaum et al. conducted a cohort study of Swedish population. A total number of 3,250,787 workers were identified from all members of the Swedish population who were employed and worked 20 hours or more per week in 1970. Participants were followed for 18 years from 1971 to 1989 or to the date of their death. Cancer cases were recognized from Swedish Cancer Register. No increased risk of breast cancer was found among night shift workers (27).

In a case-control study by Pesh et al. in 2010, 857 breast cancer cases were selected from those who enrolled in the major hospitals of the greater Region of Bonn and 892 controls were selected from population registries of the study region and they were interviewed. No association between night shift (OR=0.91 and 95% CI=0.55 to 1.49) or having ever done shift

(OR=0.96 and 95% CI= 0.67 to 1.38) and risk of breast cancer was found. This study found that working 806 night shifts or more during the life time was associated with an increased risk of breast cancer but the association was not statically significant (28).

In three of the studies reviewed (Wang et al., Menegaux et al. and Lie et al.), a significant association between night shift work and breast cancer was observed.

In a study performed by Wang et al. in 2015, 712 newly diagnosed breast cancer patients and 742 controls were entered the study and were interviewed. Cases were selected from hospitals and Yat-sen University cancer center between 2010 and 2012. Controls were selected from women who attended a health checkup in the same hospitals during the same period. They concluded that night shift workers had significantly increased risk of developing breast cancer (OR=1.34 and 95% CI= 1.05 to 1.72). Also, women with shorter than 6 hour sleep (OR=1.53 and 95% CI= 1.1 to 2.12) or longer than 9 hour sleep (OR=1.59 and 95% CI= 1.17 to 2.17) had an increased risk of breast cancer. Moreover, longer sleep duration had a significant relationship with breast cancer risk (OR= 1.63, 95% CI=1.14 to2.34). Daytime napping significantly reduced the risk of breast cancer among shift workers (OR= 0.57, 95% CI= 0.36-0.9) (29).

Menegaux et al. found a significant association between overnight work and breast cancer (OR= 1.35, 95%CI= 1.01 to 1.80). Also, duration of night work 4.5 or more years was associated with breast cancer risk (OR=1.4, 95% CI= 1.01 to 1.92). Among night shift workers, working less than 3 nights per week was significantly associated with breast cancer risk (OR=1.43, 95% CI= 1.01 to 2.03), whereas this association was not observed in those with more than 3 nights per week. In the analyses combining duration of night work and average number of nights per week, the significant association was observed between night work of long duration (4.5 years or more)

working less than 3 nights per week averagely and breast cancer risk (OR=1.83, 95% CI= 1.15 to 2.93). Menegaux et al. suggested that more frequent alteration between night and day shifts in those who worked less than 3 nights per week may cause more circadian disruption that may increase risk of breast cancer among them. (30).

Lie et al. did a nested case-control study within a cohort study of 49402 female nurses of Norway. On the multivariate logistic regression, there was a significant association between the risk estimates for breast cancer and working at least 5 years with at least 6 or 7 consecutive night shifts (OR= 1.8 and OR= 1.7 respectively). Also, a significant positive trend was observed between duration in jobs including a minimum of 6 or 7 consecutive night shifts and breast cancer risk (p=0.01 and p=0.05 respectively) (31).

In a study done by Knutsson et al. women who had night shift were in higher risk of developing breast cancer in comparison to women who did not have night shifts (HR= 2.02, 95% CI 1.03-3.95). The duration time of breast cancer diagnosis was significantly shorter in night shift workers in comparison to day workers (p=0.01), which may show that night shift may accelerate the tumor progression (32).

Two out of nine studies showed a borderline association between night shift work and breast cancer (Hansen et al. and Popantoniou et al).

In a study that was done by Hansen et al. that was a case-control study nested within a cohort of 18551 women who were employed in military. 218 cases of breast cancer and 899 controls were documented. They could find a positive association between ever shift work and cancers (OR= 1.4 and 95% CI= 0.9 to 2.1). The risk of breast cancer increased with increasing the number of years of night shift work (33).

Similarly, in a study done by Popantoniou et al, a positive none significant association was observed between having ever shift work and risk of breast cancer (OR=1.18, 95% CI= 0.97 to 1.44). Also, working for 15 or more years in permanent night shifts was associated with breast cancer risk with an OR of 1.49 (95% CI= 0.88 to 2.53) (34).

Endometrial cancer

One of the most important risk factors for endometrial cancer is increasing the level of estrogen which may happen due to obesity, or postmenopausal hormone use (35). Night shift work may increase the level of estrogen through the effect of light on decreasing melatonin level. Also, melatonin may cause endometrial cancer through other mechanisms. It may regulate aromatase activity and be a factor in fat metabolism (36-39).

In this review, only one original article about the relationship between night shift and endometrial cancer was found that met our inclusion criteria (Table 2). It is a cohort study of 5,3487 nurses who were enrolled in the Nurses' Health Study since 1976 and were followed up till 2004. Women who were diagnosed as having invasive endometrial cancers since 1988 were considered as cancer cases in this study. There was a significant association between total years of working on rotating night shifts and risk of endometrial cancer (p= 0.04). Women who worked 20 years or more in rotating night shifts had a 47% greater risk of endometrial cancer in comparison to women who never had worked night shifts (Multivariate relative risk=1.47 and 95% CI= 1.03 to 2.1). Moreover, they observed more than 2-fold increased risk of endometrial cancer among night shift workers who had BMI>30 (p=0.003) (40).

Ovarian cancer

Another cancer that women in night shift are at risk of is ovarian cancer. Two studies in this review explored the association between night shift work and the risk of ovarian cancer (Table 2). The study designs of the studies were different.

In one of the studies done in US, 181548 nurses participated in two cohort studies (started in 1976 and 1989) and they were followed for 20 years. Rotating night-shift was defined as having at least 3 nights per month, in addition to day or evening shifts. The data collection method was questionnaire. Combining both cohorts, a positive borderline association between duration of rotating night shift and risk of ovarian cancer was found (41).

The second study that had our inclusion criteria was done by Bhatti et al. 2013. 1101 women with invasive epithelial ovarian cancer and 389 women with borderline epithelial ovarian cancer from 13 areas of Washington State from 2002 to 2009 were eligible to move in the study. They were identified through a population-based cancer registry. Controls were 1832 women who were selected by random digit dialing. A positive association between working as the night shift and risk of invasive epithelial cancer was found (OR=1.24, 95% CI 1.04 to 1.49). Night shift increased the risk of invasive epithelial ovarian cancer by 1.24 fold. Also, night shift work was associated with a 1.48-fold increased risk of borderline epithelial ovarian cancer (95% CI= 1.15 to 1.90) (42).

Discussion

This review discusses the results of studies on the association between shift work and the risk of developing female cancers. We included twelve studies, most of which were about the

association between night shift and risk of breast cancer (table 2). In six out of nine studies of breast cancers, the risk was positively increased while in three studies no increased risk was observed. In the Swedish cohort study done by Schwartzbaum et al. no association was shown between night shift and the risk of breast cancer (27). One of the causes of the failure to find the association may be that their exposure was categorized according to the proportion of people in each job category. So, misclassification of exposure possibly caused an error in risk calculation. Also, the small proportion of women (0.3%) who were categorized as night shift workers possibly influenced the association (27).

Another study that showed no significant association between night shift work and breast cancer risk, was done on a population of Chinese women (26). Recent studies have shown different responses to night shiftwork in different ethnic groups (43). So, it may be concluded that genetic varieties may influence the body response to night shift work. However, more research is needed to be done in this area.

In another study by Pesh et al. no association was found between night shift work and breast cancer but long-term night shift work was found to be associated with a modestly breast cancer risk. However this association was not statically significant. In this study, the prevalence of shift work was low (7.3% of cases and 7% of controls) (28). In West Germany women were prohibited to work as night shift workers in industries until 1992. So, still the prevalence of night shift work is low among women and the most night shift workers are employed in health care and service industries not in other sectors (28). The low prevalence of women employed as night shift workers might influence the result of this study.

Six of the studies were included in this study showed a positive association between night shift work and breast cancer (29-34). Hansen et al. OR=1.4 (95% CI= 0.9 to 1.2), Wang et al. OR= 1.34 (95% CI= 1.05 to 1.72), Knutsson et al HR=2.02 (95% CI= 1.03 to 3.95), Lie et al. OR= 1.8, 95% CI= 1.1 to 2.8) for at least 5 year duration with at least 6 consecutive night shifts, Menegaux et al. OR= 1.35, (95% CI= 1.01 to 1.80), and Popantoniou etal. OR= 1.18, 95% CI= 0.97 to 1.43).

Inconsistent findings from the studies may be explained by variation in the study design and shift work definitions. The definitions of shift work in the studies have been summarized in table 3. Epidemiological studies used diverse definitions of nightshift work and the duration of shift work is different. So, these kinds of studies have the lack of standardization of exposure assessment. Also, there are differences between night systems among occupations. In the studies that all the study population is employed in one occupation the exposure is the same in all of the population. In the study done by Hansen et al. all the participants are military members and night shift work definition are the same among them. Also, in the studies done by lie et al, Viswanathan et al., and Poole at al. whose populations were selected from nurses, the exposure misclassification is not a big issue. But the problem of exposure misclassification can be more obvious when a study recruits participants from various occupations.

Moreover, in some of the studies, being a shift worker was assessed through self-reporting and was not confirmed with documented reports. So, it may cause overestimation of exposure (shift work). Also, when the exposure to shift work is measured by questionnaire or interview, respondents characteristics may influence the results of the study (6).

One other possible explanation for the inconsistency of the results of the studies can be due to age differences or menopausal status of study populations. Wang et al. concluded that the

increased risk of breast cancer in night shift workers was more apparent in premenopausal than postmenopausal women (29). It can be explained by the anti-estrogenic effect of melatonin. In night shift workers who have lower melatonin levels, increasing the gonadotrophin hormones causing higher estrogen levels especially in premenopausal women resulting in higher breast cancer risk (44). Also, Menegaux et al. found that the risk of breast cancer might be higher if night work occurs before the first childbirth when the mammary gland is not completely differentiated. It explains that hormonal changes related to circadian disruption may increase the breast cancer risk.

Furthermore, as the studies have been done in different countries, misclassification for breast cancer diagnosis might have happened. However, in most of the studies the cancer diagnosis were confirmed histologically and this misclassification might happen rarely.

One of the potential mechanisms for the increased risk of breast cancer among night shift workers is the high chance of exposure to light at night in night workers (10). Exposure to light at night may decrease melatonin secretion from the pineal gland, which peaks in the middle of night. Hahn in 1991 observed that blind women were at lower risk of breast cancer since their melatonin secretion was not affected by light (45).

In addition to the effect of shift work on breast cancer risk, the duration of shift work may be important. In the study done by Pronk et al. the duration of exposure was not associated with breast cancer (26). In other studies that showed a positive relationship between night shift and cancer, the duration of exposure was associated with breast cancer risk. In the study done by Menegaux et al. breast cancer risk was increased for duration of night shift work of 4.5 years or more (30). In the study by Hansen et al. 2- fold increase in OR was observed for duration of 6

years of night shift work or more (33). In a study by Lie et al. nurses who worked 5 years or more in 6 or 7 consecutive night shifts were significantly at higher risk of developing breast cancer (31). In a study done by Popantoniou et al, duration of 15 years or more in permanent night shift was associated with breast cancer risk (34). So, in most of the studies we reviewed, more years involving in night shift work could increase the risk of breast cancer. A study by Schernhammer et al. which its data was collected from two large prospective cohorts, "the Nurses' Health Study cohorts", supported our findings. They studied the correlation between night shift work duration and urinary 6 sulfatoxymelatonin and plasma estradiol. The results of the study showed that increasing duration of night shift works (15 years or more) significantly increased level of estradiol which is related to breast cancer risk (46).

Furthermore, some studies have suggested that inadequate vitamin D may increase risk of breast cancer (47). It has been hypothesized that some of the increased risk of breast cancer may be due to the less exposure to the sun resulting in inadequate vitamin D. Only one study, we reviewed included the information on sunbathing habits (self-reported sun-exposure). A weak protective effect of sun-exposure on breast cancer risk was observed which confirmed vitamin D hypothesis (33).

For the association of night shift and ovarian cancer, we found only one study. It showed that women worked rotating night shift for a long duration had an increased risk of endometrial cancer, particularly if they were obese (40). One of the mechanisms behind this association may be the effect of melatonin. Melatonin may have an effect on fat metabolism. Previous studies have shown that high BMI and increased adiposity can increase the risk of endometrial cancer (35). Several mechanisms may account for this event, which show the role of melatonin in fat

metabolism. In rodents, postprandial intestinal motility is shorter during the dark phase in comparison to light phase causing more weight gain in animals with shorter day hours than normal day hours (48). In human studies, women who took exogenous melatonin could lose their weight (38). Also, melatonin may cause weight loss through decreasing the appetite (49). From previous studies we may conclude that one of the effects of the low melatonin on high incidence of endometrial cancer is through its effect on fat metabolism.

Another female cancer that may be affected by night shift work is ovarian cancer. In this review we could include two studies (one cohort and one case control) (41, 42). The results of these two studies were contrast in showing the significant association between night shift work and ovarian cancer. In the cohort study done in US, no significant association was observed between night shift work and ovarian cancer. In the study that was done by Bhatti et al, they concluded that night shift work was associated with increased risk of both invasive and borderline ovarian cancers (42). One of the possible explanations for the nonsignificant association in the first study is that the duration of rotating night shift work was not updated in nurses' Health Study which might cause a misclassification of duration (41). Another explanation comes back to the definition of night shift including rotating night shift work. In this study women who had less than 3 night shifts at a week and those with constant night shift work were not included. As the results of these two studies were in contrast, further research is needed. However, for rare diseases such as ovarian cancer, cohort studies may lack power to detect significant association and case-control studies are preferred.

Overall, most of the studies in this review did not capture data on rotating versus fixed night shifts. In the IARC evaluation, studies about rotation night shifts and cancer were regarded as

notable studies and rotating night shift was shown to be more disruptive than regular fixed night shifts (2). So, in most of the studies we included, this aspect was missed resulting in misclassification of exposure.

The inconsistent findings that were observed may be due to the genetic differences. It has been suggested that shift work may influence chronotype differently (in morning type and evening type people). So, on one hand, it has been hypothesized that evening type people who may self-select to work in night shifts may be genetically more susceptible to cancers than morning type people (50). On the other hand, due to the chronotype differences, the capacity of night workers to adapt to night work schedules has been different and it has been suggested that morning type people who work at night and cannot easily adapt with working through nights, may be at higher risk of cancer than evening type people (51). The studies included in this review, were conducted in different countries, US, Europe and China which their study population may have different genetic characteristics. Recent study done in 2008, has shown ethnic variability in different circadian gene variants (52). So, the possibility of genetic differences in response to night shift has been increased. However, westernized lifestyle which may influence different cancers is becoming more common in different countries, which complicate the effect of genetic varieties in the incidence of cancers including female cancers. Although, no studies about the relationship of night shift and female cancer in developing countries were found to have our inclusion criteria and can enter this review. In developing countries lack of proper organizations and irregular work hours cause that some workers face higher hours of shift work. So, more studies are needed to be done in these countries that we can observe their shift characteristics and also we can assess the effect of genetic or other

geographical characteristics and different lifestyle in the relationship between night shift work and female cancers.

Limitations

While studying the effect of night shift work on female cancers, we confront different confounders that should be controlled. However, as female cancers are multifactorial diseases and some of their reasons may be unknown, in none of the studies all the confounders could be controlled. Moreover, as participants of some of the studies were recruited from different jobs, other known or unknown carcinogenic occupational exposures could possibly influence the results of this study. As case-control studies are retrospective and in some studies a long time has passed since the exposure, recall bias is one of the important sources of bias in these studies. Also, in case-control studies, people who have cancers in comparison to healthy participants might have been more sensitive and report exposure more than controls.

A 'healthy worker effect' that workers who experienced health problems tended to leave that type of work possibly resulted in another type of bias.

In most of the studies, only live cancer cases were included in the study. So, more aggressive and fatal cases of cancers might be ignored.

Conclusion

This review provides evidence to support the positive association between night shift work and some female cancers. However, the numbers of studies about the association between night shift and endometrial and ovarian cancers was low. Furthermore, all the studies were

observational studies, and the possibility that other health and lifestyle factors associated with night shift work could increase breast cancer risk still can't be ruled out. In all of the studies that we reviewed, exposure was assessed subjectively. So, studies in which exposure is measured in an objective way are needed to be done. Also, future studies including control trials need to be done about the association of night shift work and endometrial and ovarian cancers. Validation studies of interview and questionnaire data are needed to find out if and, to what extent, recall bias occurs.

Implications and recommendations for public health practice and/or policy

The results of this review can be used for different clinicians. For future studies in this field, we recommend high quality cohort studies to be done and all the information on the following characteristics should be gathered:

- shift work schedules, including duration and frequency of night work
- diverse occupations
- age on the nightshift
- the frequency and amount of night work per month or per year
- rotating or fixed shifts
- start and finish time of the night work
- exposure to light at night
- sleeping times and napping times
- geographic areas

Also exposure should be measured in an objective way before the disease has occurred, ideally in cohorts with long follow-up. Validation studies of interview/questionnaire data are needed to be done.

Also, the effect of genetic polymorphisms on the relationship of night work and cancer should be evaluated.

If we can prove the effect of melatonin on female cancers through more research, then some solution such as taking exogenous melatonin may help to reduce these kinds of cancers. Also, the anti-estrogenic effect of melatonin can make exogenous melatonin a useful replacement for hormonal therapy.

Critical reflection

Through the capstone project, I could employ the skills and knowledges I learned through the MPH program in this review paper. The skills included systematic research, literature aggregation and interpretation according to the type of the study, and critical appraisal of the literatures. Through this project, I reviewed papers with different designs and I learned that every design has its weaknesses and strengths. However, for those who want to do the same research, I recommend doing the systematic review and meta-analysis that allow the results of different studies to be evaluated together.

Through completing this review, I understood that when the association between night shift work and female cancer is proved with more research, suitable interventions, limitations of each of them and their cost should be considered.

This project is a literature review and I concluded that the power of literature review in extracting the recommendations is low. Nevertheless, the recommendations that I can suggest after completing this project may be detecting high risk women and lowering the number of their night shifts. Also, earlier screening for female cancers and more frequent diagnosing tests are recommended for these high risk women. Training workshops for women who are night shift workers about early symptoms of female cancers, the influence of doing regular breast self-exam, regular physical exam by doctor, mammography, and regular Pap smear in early diagnosis and effective treatment of cancers may be recommended.

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Table 1. Checklist for quality assessment of studies

Type of studies	checklist	Classification of studies
Case-control studies	Diagnosis of cases	One star: medical records, cancer registry, or histopathology zero star: no description
	Selection of controls	One star: free of cancer zero star: no description
	Definition of night work	One star: was defined zero star: no description
	Same method for prove of exposure	One star: yes zero star: no
	Adjustment	Two stars: control for 8 or more of confounders One star: control for 4 ≤n<8 of confounders zero star: control for less than 4 confounders
	Non-response rate	One star: <30% and same rate for both groups zero star: >30% or different rate or no description
Cohort studies (or nested case-control studies in which exposure was prospective)	Free of cancer at starting	One star: yes zero star: no description
	Definition of night work	One star: was presented zero star: no description
	Diagnosis of cancers	One star: medical records, cancer registry, or histopathology zero star: no description
	Follow up duration	One star≥ 10 years zero star< 10 years or no description
	Adjustment	Two stars: control for 8 or more of confounders One star: control for 4 ≤n<8 of confounders zero star: control for less than 4 confounders
	Follow-up rate	One star≥ 80% zero star< 80% or not reported

Table 2. Characteristics of included studies assessing the relationship between night shift and female cancers

Study (Author, year)	Cancer type	Design	Source of participants	Number of participants	Mean age (year)	Location	Occupations	Night shift prevalence (%)	Source of information	OR/RR/HR/SIR (95% CI)
Wang et al 2015	Breast	Case-control	Cases and controls from hospital	712 cases and 742 controls	47.6 for cases and 47.4 for controls	China	Various	33% of cases and 26.2% of controls	Interviews	1.34 (1.05-1.72)
Knutsson et al. 2012	Breast	Cohort	Public and private companies	4036 women	43.5	Sweden	Various	13.6% of participants	Questionnaire	2.02 (1.03-3.95)
Menegaux et al. 2013	Breast	Case control	Cases from hospitals of specific areas of French, controls from general population of the same areas	1232 cases and 1317 controls	49	France	Various	12.9% of cases and 11.1% of controls	Interview	1.35 (1.01-1.80)
Lie et al. 2010	Breast	Nested case-control	Nursing school	699 cases and 895 controls	54	Norway	Nurses	85% of cases and 84% of controls	Interview	1.8 (1.1-2.8)
Papantoniou et al. 2015	Breast	Case-control	General population	1708 cases and 1778 controls	58.5 for cases and 56.2 for controls	Spain	Various	15.8% of cases and 13.3% of controls	Interview	1.18 (0.97-1.43)
Hansen et al. 2012	Breast	Nested case-control	Danish military	2018 cases and 899 controls	<70	Denmark	Military	31% of cases and 26% of controls	Questionnaire and interview	1.4 (0.9-2.1)
Pronk et al. 2010	Breast	Cohort	Representative communities	73049	52.5	China	Various	44% of participants	Interviews and job exposure matrix	1 (0.9-1.2) in job exposure matrix 0.9 (0.7-1.1) in interview
Pesh et al 2010	Breast	Case-control	Residents of Greater Region of Bonn, Germany	857 cases and 892 controls	56	Germany	Various	7.3% of cases and 7% of controls	Interview	0.91 (0.55-1.49)

Schwartzbaum et al 2007	Breast	Cohort, retrospective	Randomly sample of employed people in1960 and 1970	3,250,787	57	Sweden	Various	0.3% of women in occupations in which 40% stated that were shift workers	Interview and consensus	0.94 (0.74-1.18)
Viswanathan et al. 2007	Endometrial	Cohort	Nurses	53487	55	US	Nurse	59%	questionnaire	1.47 (1.03-2.1)
Bhatti et al. 2013	Ovarian	Case-control	female residents of 13-county area of western Washington	1101 with invasive , 389 with borderline and 1832 controls	–	US	various	26.6% of invasive, 32.4% of borderline cases and 22.5% of controls	interview	1.24 (1.04-1.49) for invasive 1.48 (1.15-1.9) for borderline cancer
Poole et al. 2011	Ovarian	2 cohort (NHS and NHSII)	Nurses	181548	55.7	US	Nurse	59%of NHS and 67.8% of NHSII had ever night shift	questionnaire	1.28 (0.84-1.94)

Table 3. Definitions of night work in the studies

Study (Authors, year)	Definition of night shift
Pronk et al. 2010	Starting work after 10 PM at least 3 times a month for over 1 year
Hansen et al. 2012	During hours beginning 17 and ending before 9:00, not including overtime for at least 1 year
Wang et al. 2015	Being awake or working between midnight and 6:00 AM
Pesh et al. 2010	Working the full time period between 24:00-5:00 hours
Schwartzbaum et al. 2007	Working any hours between 1:00 and 4:00 at least 1 day during the week preceding the interview
Knutsson et al. 2012	Working between 22 pm-6 am
Menangaux et al. 2013	At least 1 hour between 11:00 pm and 5:00 am during all or part of each job
Lie et al. 2010	Shift that lasted from at least 12 PM until 6 AM, although the shift may start earlier or end later
Popantoniou et al. 2015	Working schedule that involved partly or entirely working between 00:00 and 6:00 am at least three nights per month.
Viswanathan et al. 2007	Rotating night shifts as working at least three nights per month, in addition to daytime or evening shifts in that month
Poole et al. 2011	Rotating night shifts at least 3 nights per month in addition to day or evening shifts
Bhatti et al. 2013	Hours between midnight and 4:00

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