

Does Circadian Rhythm and Environment Factor Affect the Risk of Breast Cancer? A New Evidence from Kediri, East Java

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ABSTRACT

Background: Disruption of sleep patterns, and thereby the internal body clock, of shift workers directly influences their physiology and the rate of cancer development. Studies have shown that working night shifts three or more times per month elevates the risk of breast cancer in humans. Disrupted expression of circadian genes can alter breast biology and may promote cancer. This study aimed to examine the effects of circadian rhythm and environment factor on the risk of breast cancer in Kediri, East Java.

Subjects and Method: This was a case-control study conducted in Kediri, East Java, from April to May 2018. A sample of 200 women was selected by fixed disease sampling. The dependent variable was breast cancer. The independent variables were work schedule, sleep duration, room light, room temperature, chemical exposure, and air pollution. The data were collected by questionnaire and analyzed by a multiple logistic regression.

Results: Circadian rhythm and environment factor affected the risk of breast cancer. The risk of breast cancer increased with irregular shift work schedule (OR= 5.82; 95% CI= 2.26 to 14.95; $p < 0.001$), sleep duration < 5 hours (OR= 6.32; 95% CI= 2.59 to 15.39; $p < 0.001$), room light (OR= 7.03; 95% CI= 2.39 to 20.65; $p < 0.001$), warm room temperature (OR= 13.48; 95% CI= 5.26 to 34.53; $p < 0.001$), air pollution (OR= 8.21; 95% CI= 3.19 to 21.11; $p < 0.001$), and chemical exposure (OR= 2.90; 95% CI= 1.22 to 6.84; $p = 0.015$).

Conclusion: The risk of breast cancer increased with irregular shift work schedule, sleep duration < 5 hours, room light, warm room temperature, air pollution, and chemical exposure.

Keywords: breast cancer, circadian rhythm, environment factor

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BACKGROUND

Breast cancer is a type of cancer with the highest frequency in the world that usually occurs in women (Richard, 2009). Data from the International Agency for Research on Cancer (IARC) show that in 2012, there were 14,067,894 new cases of cancer and 8,201,575 cancer deaths worldwide, and breast cancer was the highest cause of death by 43.3% (WHO, 2016).

Breast cancer is also the highest cause of female death due to cancer in Indonesia.

According to the Basic Health Research (Riskesmas) the number of breast cancer cases in Indonesia was 61,682 cases (Riskesmas, 2013). In 2015, the proportion of female deaths caused by breast cancer increased to 16%, while the prevalence of breast cancer in women in Indonesia in 2016 was 2.1% (Ministry of Health RI, 2016). This situation requires appropriate handling efforts to avoid an increase in the female mortality rate caused by breast cancer (Ministry of Health RI, 2016).

Cases of breast cancer in Indonesia are mostly found in Java. Health Service data states that East Java is the region with the highest number of suspicious breast cancers in Indonesia (East Java Provincial Health Office, 2015). This is related to the high number of female population, which is 19.79 million people (BPS East Java, 2016). Breast cancer is also the second leading cause of death in women in East Java in 2015 with a proportion of 1.66% of all maternal deaths. Meanwhile, the prevalence of breast cancer in women is 3.66% (East Java Provincial Health Office, 2015).

Kediri Regency is included in 5 regencies with the highest prevalence of breast cancer in 2016. The prevalence of breast cancer in women is 215 cases per 244,437 women. This amount compared to 2015 experienced an increase of 0.6%. 515 cases of female deaths were also found in Kediri Regency and 30% of the total deaths of women were caused by breast cancer (DHO, Kediri District Health Office, 2016).

Breast cancer occurs because of the interaction of several components or risk factors. Epidemiological studies have proven that conventional risk factors for breast cancer account for up to 50% of breast cancer cases in the world. 1% of breast cancers found in other countries can be associated with diagnostic radiotherapy. In the late 1990s, several studies concluded that more than 60% of breast cancers have an environmental etiology. Breast cancer is most likely to occur due to complex interactions between genetic, endocrine, and environmental factors (Loreta et al., 2010).

Cancer or malignant tumor is the growth and spread of cells/ tissues that do not control, continue to grow or increase, immortal (unable to die) (Ministry of Health RI, 2015). Breast cancer is a

carcinoma originating from the ducts or lobules of the breast (Vighnesh et al., 2013).

Statistical data in 2016 showing that 50% of the world's population of women of reproductive age had their own job (International Labor Organization, 2016). Working that is not balanced with the correct circadian rhythm will cause risk factors for breast cancer (Johni, 2014). In Kediri district, the population of women who have jobs according to the Central Statistics Agency (BPS) data is 58.24%, and those who work more than 35 hours a week are 72%. The dominating work of women is as factory workers, civil servants, and entrepreneurs (BPS Kediri Regency, 2016). The high number of female workers ishand in hand with the high incidence of breast cancer in the district of Kediri. The results of research conducted by Steven (2009), Pronk (2010), and Hansen (2014) show that the factors that influence the incidence of breast cancer in women in the global era are due to uncontrolled circadian rhythms. Circadian rhythm is a term used to describe the organism's lifestyle every day (Alan, 2013).

Literally, circadian rhythm means a cycle that lasts about 24 hours (in Latin *circa* means around, *dian* means one day or 24 hours) (Josef, 2014). Circadian rhythm factors that indirectly affect women's health associated with breast cancer include the division of work hours performed by women, the duration of sleep that is not in accordance with the standards of human rest needs, and the influence of light when resting at night (Johni et al., 2012). In a study conducted by Johni (2014), night work can interfere with circadian rhythms, by suppressing the production of the hormone melatonin and resulting in sleep deprivation, all which affect hundreds of metabolisms and physiological processes, including production hormones (Johni,

2014). The role of circadian rhythms is not itself a high risk factor for breast cancer in women in the world, environmental factors also have an influence on the health status of its population, including its effect on the risk of the incidence of breast cancer of female workers as vulnerable (Loreta et al., 2010). Environmental factors are very concerned because it deals directly with individual activities every day such as exposure to UV radiation, presence of electromagnetic fields, exposure to pesticides, radiation exposure to activities that use ions, exposure to cigarette smoke, pollution, and the presence of carcinogens in the workplace (David et al., 2015).

Seeing many risk factors that affect breast cancer and the high mortality rate from breast cancer in women, the breast cancer prevention strategy is important for each country to support the achievement of the goals of Sustainable Development Goals (SDGs) in reducing women's morbidity and mortality especially in global era in which they have jobs and can provide advice to the government in improving policies on female workers in Indonesia. Based on the background above, the researchers are interested in conducting research on the effects of circadian rhythms and environmental factors on the risk of breast cancer in female workers.

SUBJECTS AND METHOD

1. Study Design

This was an analytic observational study with a case control design. The study was conducted in Kediri, East Java, from April to May 2018.

2. Population and Samples

The source population was divided into two, namely women who suffer from breast cancer and women who do not suffer from breast cancer. A sample of 200 women was selected by fixed disease sampling.

3. Study Variables

The dependent variable was breast cancer. The independent variables were shift work schedule, sleep duration, room light, room temperature, chemical exposure, and air pollution.

4. Operational Definition of Variables

Breast cancer was defined as a cancer suffered by a diagnosed patient based on histopathology of tissue biopsy. The data were taken from medical record.

Shift work schedule was defined as a form of scheduling that requires individual workers or workers who are members of a team to work alternately in the same work area at the same time or at different times so that operations can run continuously for 24 hours. In this work shift system, workers will be divided into morning work (07.00-14.00 WIB), afternoon (14.00-21.00 WIB) and evening (21.00-07.00 WIB).

Sleep duration was defined as the total hours of sleep for a day which is the accumulation of sleep during the day and night. This sleep will be grouped according to Self-report duration sleep.

Room light was defined as light that comes from a lamp that is used by the subject while sleeping.

The room temperature was defined as the state of heat or not a room that supports a person's level of comfort during sleep. Data on room temperature was measured by a room thermometer.

Exposure to chemicals is materials that contain chemicals that are included in carcinogens (chemical carcinogens namely benzopyrene, polycyclic aromatic hydrocarbons, heavy metals, chromium (Cr), nickel (Ni), uranium (Ur), cadmium (Cd), hair dyes, cosmetics).

Air pollution was defined as air pollutants obtained by the subjects represented by an overview of the environment around

the house and workplace (vehicle smoke, chimney smoke, and combustion smoke).

5. Data Analysis

Univariate analysis was carried out to examine the frequency distribution and the percentage characteristics of the study subjects. Bivariate analysis was conducted to investigate the relationship between dependent and independent variables by chi-square test. Multivariate analysis was performed using logistic regression.

6. Research Ethics

The research ethics includes informed consent, anonymity, confidentiality, and ethical clearance. The ethical clearance in this study was conducted at Dr. Moewardi hospital, Surakarta.

RESULTS

1. Study Subject Characteristics

The study subjects were 207 female workers. Case group (women with breast cancer) amounted to 86 people and 121 people in the control group (women who did not have breast cancer).

2. Bivariate analysis on the risk of breast cancer

Bivariate analysis was used to examine the relationship between shift work schedule, sleep duration, room light, room temperature, chemical exposure, air pollution, and breast cancer. The results of bivariate analysis can be seen in Table 2.

Table 1. Study Subject Characteristics

Variable	n	%
Work Schedule		
Regular	137	66.2
Irregular (shift)	70	33.8
Sleep Duration		
Lack of Sleep (<5 hours)	91	44.0
Enough Sleep (5-9 hours)	116	56.0
Room Temperature		
(31°C-37°C)	110	53.1
(20°C-30°C)	97	46.9
Room Light		
Low	157	75.8
High	50	24.2
Chemical Exposure		
Low (<4)	112	54.1
High (>4)	95	45.9
Air Pollution Exposure		
Low (score <3)	105	50,7
High (score >3)	102	49,3

Table 2. Bivariate Analysis on the Risk of Breast Cancer

Independent Variable	Breast Cancer				OR	95% CI	p
	No		Yes				
	n	%	n	%			
Shift work schedule							
Regular	90	74.4	47	54.7	2.40	1.33 to	<0.001
Irregular (shift)	31	25.6	39	45.3		4.34	
Sleep Duration							
<5 hours	30	24.8	61	70.9	0.13	0.07 to	<0.001
5-9 hours	91	75.2	25	29.1		0.25	
Room Temperature							
31°C-37°C	71	82.6	39	32.2	0.10	0.05 to	<0.001
20°C-30°C	82	67.8	15	17.4		0.19	
Room Light							
Low	106	87.6	51	59.3	4.85	2.43 to	<0.001
High	15	29.2	35	40.7		9.67	
Chemical Exposure							
Low (score <4)	79	65.3	33	38.4	3.02	1.70 to	0.015
High (score >4)	42	34.7	53	61.6		5.36	
Air Pollution Exposure							
Low (score <3)	78	64.5	27	31.4	3.96	2.20 to	<0.001
High (score >3)	43	35.5	59	68.6		7.13	

Table 3. The Results of a Multiple Logistic Regression on the Risk of Tuberculosis

Independent variable	b	95% CI		p
		Lower limit	Upper limit	
Irregular shift work schedule	3.66	2.26	14.95	<0.001
Sleep duration <5 hours	4.06	2.59	15.39	<0.001
Room temperature 31°C-37°C	5.42	5.26	34.53	<0.001
High room light	3.55	2.39	20.65	<0.001
High chemical exposure	2.43	1.22	6.84	0.015
High air pollution exposure	4.38	3.19	21.11	<0.001

3. Multivariate Analysis

Multivariate analysis described the effect of more than one independent variables on one dependent variable. Multiple logistic regression analysis was done by Stata 13.

Table 3 showed that the risk of breast cancer increased with irregular work shift schedule (b= 3.66; 95% CI= 2.26 to 14.95; p<0.001), sleep duration <5 hours (b= 4.06; 95% CI= 2.59 to 15.39; p<0.001), room temperature 31°C-37°C (b= 5.42; 95% CI= 5.26 to 34.53; p<0.001), room light (b= 3.55; 95% CI= 2.39 to 20.65; p<0.001), high chemical exposure (b= 2.43; 95% CI= 1.22 to 6.84; p= 0.015), and high air pollution exposure (b= 4.38; 95% CI= 3.19 to 21.11; p<0.001).

DISCUSSIONS

1. The effect of work shift schedule on breast cancer

The result of this study showed that there was a positive association between work shift schedule on breast cancer. Women with irregular work shift schedule were more likely to have breast cancer. In this study, as many as 39 women (45.3%) suffering from breast cancer. Work schedule at night became one of the determinants of breast cancer.

Job - Night work shift of the "Light at Night" theory explained that light exposure at night lead to suppression of melatonin which was circulated throughout the body (due to the displacement of the melatonin

rhythm phase) and changing levels of cortisol, estrogen, and some other androgens (Boivin *et al.*, 2014; Videnovic *et al.*, 2014).

Circadian regulation of plasma melatonin levels was very necessary for various physiological processes such as taking free radicals, regulating hormonal path, and energy balance (Kochanet *al.*, 2015). Therefore, it was not surprising that disruption of melatonin rhythm was associated with several diseases, especially cancer. Microarray studies revealed that some liver enzymes and SCN showed circadian rhythms (Stevens *et al.*, 2012a; Stevens *et al.*, 2012b) and thus regulating the metabolic conditions of the organism.

Some studies (Davis *et al.*, 2011; Schernhammer *et al.*, 2011; Hansen *et al.*, 2011; Megdalet *al.*, 2005; Hansen and Lassen, 2012) showed association between night work shift schedule and the incidence of breast cancer. This study was supported by "Light at Night" (LAN) as a potential "carcinogen". This theory was further supported by a series of studies which related "Light at Night" to changes in melatonin secretion while the result of melatonin concentration was associated with the development of breast cancer (Stevens *et al.*, 2012a; Stevens *et al.*, 2012b). As stated earlier, the LAN could reduce melatonin levels at night (Touitou *et al.*, 2017).

2. The effect of sleep duration on breast cancer

The result of this study showed that there was a positive association between sleep duration and breast cancer. Circadian rhythm can be maintained in the absence of a trigger source, but circadian synchronization occurred when the internal oscillations were not parallel to the external environment. It could also lead to hormone release disorders such as melatonin which was covered by light signals that affected sleep duration in inappropriate time results when the suppression phase of melatonin was not released at the usual time (Yuet *et al.*, 2011).

Removing hormones such as melatonin has an important effect on breast cancer. This hormone reduction increased the risk of cancer. Because sleep quality was the main factor for synchronizing internal and external rhythms, the amplitude/ duration of serum melatonin rhythm depend on the length of the resting time (Torpyet *et al.*, 2009).

3. The effect of room temperature on breast cancer

The result of this study showed that there was a positive association between room temperature and breast cancer. Circadian rhythms were biological rhythms that rearrange the body's functions every 24 hours (the Latin term was "circa" (around), and "diem" (days). This 24-hour system existed in many forms of life on earth and was preserved throughout evolution (Blakeman *et al.*, 2016). In humans, circadian rhythms were accelerated in body functions with levels of diurnal and nocturnal activity, by regulating hormones, body temperature, cell metabolism, and cell growth (Wang Pan *et al.*, 2015).

The classical phase signals of a biological clock were body temperature, the level

of the hormone cortisol, and melatonin (Boumans *et al.*, 2017).

The rhythm was able to be reset by an external stimulus such as light. However, in the unavailability of external stimulation such as the room temperature at resting time which the rhythm was maintained for almost 24 hours (Samuelsson *et al.*, 2018).

4. The effect of room light on breast cancer

The result of this study showed that there was a positive association between room light on breast cancer. Indoor lighting was not as effective as sunlight in absorbing the circadian oscillator because of the low intensity and possibly due to the strong spread of energy in the body. Previous studies showed that artificial light was sufficient enough to make visual acuity, but it might not be enough to make circadian rhythms to be more efficient, which resulted in chronic circadian misalignment (Stevens *et al.*, 2012a; Stevens *et al.*, 2012b).

The characteristics of sunlight intensity were unique and most efficient in stimulating retinal ganglion cells, which involved the wave length and intensity of the circadian clock depending on the way to get the light (Stevens *et al.*, 2012a; Stevens *et al.*, 2012b).

Artificial light was widely used in developed and industrial countries. While developing and underdeveloped countries did not use artificial light. The high risk of major complex diseases such as metabolic syndrome and cardiovascular disease in Indonesia including developed countries clearly supported the possibility of this association (Yu *et al.*, 2011).

5. The effect of chemical exposure on breast cancer

The result of this study showed that there was a positive association between chemical exposure and breast cancer.

Previous studies reported that the risk of breast cancer due to radiation was affected by the dose received, age at the time of exposure to radiation, the length of exposure, gender, and genetic factors. Women who conduct mammographic examinations were 4 times more likely to have cancer. According to Vogel, a low dose was associated with an increased incidence of solid tumors such as breast cancer (Levandovski *et al.*, 2013).

Women who have a history of chemical exposure since adolescence (cosmetic use) were more likely to have breast cancer (Shanmugam *et al.*, 2013).

6. The effect of air pollution exposure on breast cancer

The result of this study showed that there was a positive association between air pollution exposure on breast cancer. History of pollution exposure was thought to have an effect on the enhancement of the risk of breast cancer. Exposure to estrogen from the environment in the form of organochlorines in pesticides and the chemical industry might contribute to the incidence of breast cancer. Several studies have reported an enhancement in levels of 1,1-dichloro 2,2-bis (p-chlorophenyl) ethylene (dde) and polychlorinated biphenyls (PCBs) in breast cancer patients' blood (Videnovic *et al.*, 2014).

Case control study in England showed the organochlorine content in pesticides, and polycyclic aromatic hydrocarbons was associated with the incidence of breast cancer among women in Long Island. The results of the study on the relationship between pesticide and the incidence of breast cancer did not provide consistent results (Videnovic *et al.*, 2014).

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