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CHRONOTYPE IN BREAST CANCER AND RELATION TO DESYNCHRONIZATION OF THE CIRCADIAN CYCLE

O cronotipo no câncer de mama e sua relação com a dessincronização do ciclo circadiano

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ABSTRACT

Introduction: The circadian cycle plays several roles at the organism functions and are important to the maintenance of health, when synchronized. Nowadays, one of the main risk factors for the change of the sleep-wake cycle in the population is the high exposure to light at night, consequently deregulating the circadian cycle, inhibiting the release of melatonin and favoring oncogenesis. **Objectives:** The aim of this study was to identify the possible associations between circadian rhythm's desynchronization and breast cancer. **Methods:** This is a descriptive cross-sectional study and two collection instruments were used in it: sociodemographic questionnaire and the Horne and Ostberg matutinal-vespertine questionnaire. They were applied in a group of 74 women in a highly complex oncology service. **Results:** To evaluate whether the discriminant factors such as night work and chronotype exerted some influence on the discriminated factor that is breast cancer, χ^2 test was applied showing that the characteristics among the groups were similar and so it was not possible to confirm that there is a relationship between them. **Conclusions:** More studies about the subject is needed.

KEYWORDS: Breast neoplasms; circadian rhythm; carcinogenesis; melatonin.

RESUMO

Introdução: O ciclo circadiano desempenha vários papéis nas funções do organismo e é importante para a manutenção da saúde, quando sincronizado. Atualmente, um dos principais fatores de risco para a mudança do ciclo vigília-sono na população é a alta exposição à luz noturna, desregulando consequentemente o ciclo circadiano, inibindo a liberação de melatonina e favorecendo a oncogênese. **Objetivo:** O objetivo deste estudo foi identificar as possíveis associações entre dessincronização do ritmo circadiano e o câncer de mama. **Métodos:** Trata-se de um estudo descritivo de corte transversal em que foram utilizados dois instrumentos de coleta: um questionário sociodemográfico e o questionário matutino-vespertino de Horne e Ostberg. Os questionários foram aplicados a um grupo de 74 mulheres em um serviço de oncologia. **Resultados:** Para avaliar se os fatores discriminantes como o trabalho noturno e o cronotipo exerceram alguma influência sobre o fator discriminado, câncer de mama, foi aplicado o teste do χ^2, que revelou semelhança entre as características dos grupos estudados. **Conclusões:** Mais estudos sobre o assunto são necessários de forma a se compreender melhor a possível relação entre o ciclo circadiano e a susceptibilidade ao desenvolvimento de neoplasias, especialmente o câncer de mama.

PALAVRAS-CHAVE: Câncer de mama; ritmo circadiano; carcinogênese; melatonina.

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INTRODUCTION

Humans, in 24 hours per day, undergo biological processes controlled by the circadian cycle, known as biological clock, such as the regulation of sleep-wake cycles, body temperature, energy metabolism, cell cycle and hormonal secretion.[1] The timing of these processes is responsible for maintaining the individual's health. However, some internal and external factors can interfere with the regulation of this cycle, the main one being the artificial light, which increases the risk of developing certain diseases, such as breast cancer.[2]

The rhythmicity of the sleep-wake cycle varies depending on each individual's age, and thus the chronotype, which is the sleep-wake cycle associated with interindividual differences.[3] With these changes in sleep-wake cycle, there are also changes in the rhythm of temperature and nocturnal melatonin peaks in each of these phases, thus showing changes in the biological clock.[4]

The biological clock's core consists in genes that will generate and regulate the circadian rhythms within the cells throughout the individual's body.[5] These genes belong to two families: Period and Cryptochrome, and are subdivided into Per1, Per2 and Per3, and Cry1 and Cry2.[6] They are activated by transcriptional factors, known as CLOCK (Circadian Locomotor Output Cycles Kaput) and BMAL1 (Brain-Muscle Arnt-Like protein 1), that will induce the expression of these genes.[6,7]

The circadian rhythm is capable of controlling the expression of cell cycle's genes. This control is carried out through the heterodimer CLOCK-BMAL1, acting on the cell cycle's genes, such as Wee1 (which acts in the G2-M transition); cMyc (the G0-G1 transition) and cyclin D1 (in the G1-S transition).[1,8] Due to this control, heterodimer can also function as a tumor suppressor at systemic, cellular and molecular levels.[1]

Nowadays, one of the main risk factors for the change of sleep-wake cycle is the high exposure to light at nighttime.[7] According to the theory "light at night," the increased use of electric light is related to the increased risk for breast cancer.[9] The mechanism is the reduction on melatonin production, thus increasing the release of estrogen by the ovary.[10] Some studies found that the risk of cancer rises as years of work or hours per week in night shift.[9]

One of the most important studies, the Nurse's Health Study, 1987, presented the risk association between night shift at work and breast cancer,[10] following nurses over a period of ten years. According to these studies, the risk for breast cancer had a moderate increase in women who have worked at night for an average of 14 years, while those who have worked for 30 years or more, showed a very high risk.[7]

Several studies also consider biological time as a tool to improve the treatment for certain diseases, which is known as chronotherapy. The circadian rhythm can also control some drugs' metabolism, varying its bioavailability. In experimental models, both the toxicity and efficacy of over thirty anti-cancer varied according to the period in which they were administered.[1]

In Brazil, breast cancer is the most common disease in women after nonmelanoma skin cancer and has a high mortality rate due to late diagnosis.[11] Therefore, it is necessary to know the various factors involved in its genesis. The aim of this study was to identify the possible relationship between changes in the circadian rhythm and breast cancer.

METHODS

This is a descriptive cross-sectional study and two collection instruments were used in it: sociodemographic questionnaire and the Horne and Ostberg matutinal-vespertine questionnaire. These questionnaires were applied in a group of 74 women in a highly complex oncology service to treat breast cancer.

Both questionnaires were approved by the Ethics Committee of Pontifical Catholic University of Goiás. They were applied to 74 participants belonging to two groups: 40 patients with breast cancer and 34 controls (women who did not have cancer). Were included in this study women with 18 years or more seen at the Brazilian Center for Radiotherapy, Oncology and Mastology (CEBROM) in two situations:

- Those healthy, undergoing routine tests (control group);
- Those diagnosed with breast cancer (case group), who agreed to participate by signing the Informed Consent Form (ICF).

The questionnaires were applied in a highly complex oncology service in to treat breast cancer in Goiânia, Goiás, Brazil, from December 2015 to April 2016.

For comparative statistics, the χ^2 test for categorical variants and the t Student and ANOVA tests for continuous variants were used. The analyzes were made at BioEstat 5.0 software.

RESULTS

The age variation of the control group was between 21 and 70 years, with a mean of 48.6 (±12.2) years. In the case group the mean age was 54.1 (±13.2) years, with a maximum of 79 and minimum of 33 years. Both groups presented homogeneity of ages (p=0.07). In relation to weight, the variation was higher in the case group (minimum of 47 kg and maximum 110 kg), but the average was 66.3 (±13.4) kg, while the control group's average was 64.8 (±8.6) kg being the variation between 50 and 83 kg (p=0.561). Regarding BMI (body mass index), the control group had an average of 25.31 (±6.97) kg/m^2 and average for the case group was 26.22 (±6.09) kg/m^2 (p=0.552).

The age at menarche did not vary between the groups (p=0.242), being, on average, 13 (±2.0) years for cases and 13.5 (±1.7) for controls. Also, the age of menopause did not change (p=0654) between groups, being 46.8 (±4.2) years in the control and 47.7 (±6.8) in cases.

Regarding the age of first pregnancy, patients with breast cancer had an average of 26.3 (±7.3) years, with a minimum of 15 and a maximum of 38 years. In the control group, the average was 24.5 (±7.4) years and ranged from 14 to 48 years (p=0.377). About the number of children, cancer patients' average was of 1.7 (±1.5) children, and control patients' was of 1.6 (±1.2) (p=0.826). This data can be seen in Table 1.

Regarding the use of contraceptives, 15 (37.5%) patients with breast cancer did not use them, and 25 (62.5%) used. At the control group, 5 (14.7%) did not use contraceptives and 29 (85.3%) used. In relation to hormone replacement therapy (HRT), 28 (70%) patients with breast cancer and 24 (70.6%) from the control group didn't use, while 12 (30%) patients with breast cancer and 10 (29.4%) from the control group made use of HRT.

About trouble at sleeping, 18 (45%) cases and 23 (67.6%) of controls didn't have, against 22 (55%) and 11 (32.4%), respectively, reported some difficulty. When asked about the room lighting while sleeping, 5% (2) of cancer patients were sleeping in a bright room (with light), 37.5% (15) in a room with dim light and 57.5% (23) were sleeping in a dark room. In controls, the percentages were, respectively, 5.9% (2) 41.2% (14) and 52.9% (18).

Regarding family history, the following variants were analyzed: cancer family history and breast cancer in the family. In cancer patients the percentages of these data were: 85% (34) had a history of cancer in the family, 70% (28) without breast cancer history in the family. In the controls, the results were, respectively, 73.5% (25) and 58.8% (20). As seen in Table 2.

Regarding chronotype, it was observed that, from 74 patients, 23.0% fit within the profile 'definitely matutinal' (DM); 45.9% were 'moderately matutinal' (MM); 21.6% 'Intermediate' (INT); 8.1% 'moderately vespertine' (MV); and 1.4% of 'definitely vespertine' (DV). When stratified between the groups, we observed that in cases with cancer, the rate was 15% DM, 47.5% MM, INT 30%, MV 5% and 2.5% DV; controls were 32.4% DM, 44.1% MM, 11.8% INT and also MV, but presented no profile definitely vespertine (Figure 1).

Assessing the shifts in which each patient had worked, it was observed that 44.4% of the patients with breast cancer and 47.1% of the controls worked in the morning period. From those who worked in the evening shift, 42.9% were cases and 45.6% were controls; and 6.3% and 5.9%, respectively, worked on the night period. From those working full-time, 6.3% were cases and 1.5% controls. The average working time was 17 years in cases and 11.6 years in controls (Figure 2).

Data for chronotype and work shift can be seen in Table 3.

From the breast cancer patients analyzed, 70% (28) perform chemotherapy. From these, 50% (14) preferred to perform chemotherapy in the morning, 14.3% (4) preferred in the afternoon and 35.7% (10) said they were indifferent. Over the reported periods after chemotherapy, the worst collateral effects were 14.3% (4) in the morning and also in the evening; 10.7% (3) in the night; and 60.7% (17) reported being indifferent (Table 4).

DISCUSSION

Risk factors for breast cancer may be related to both endocrine factors and reproductive history, as well as with behavioral and environmental factors. Among endocrine and reproductive history factors, one of the most important is prolonged exposure to estrogen, either endogenous or exogenously.[11] Obesity and desynchronization of the circadian cycle are part of behavioral and environmental factors.

From the results, some had no major changes when compared between two groups. The average age of menarche, for example, was 13 years in patients with breast cancer and 13.5 years in controls, with a minimum age of 10 and 11 years, respectively. In a study about the influence of hormonal factors in patients with breast cancer, data from 484 patients was analyzed. They found that the average age of menarche was 13.32 years and that the later was the age of menarche, the later was the age of diagnosis[12]. Although the average age of menarche between these patients is similar to the ones in the present study, it was not possible to correlate this data with the time of diagnosis, due to the lack of this type of data.

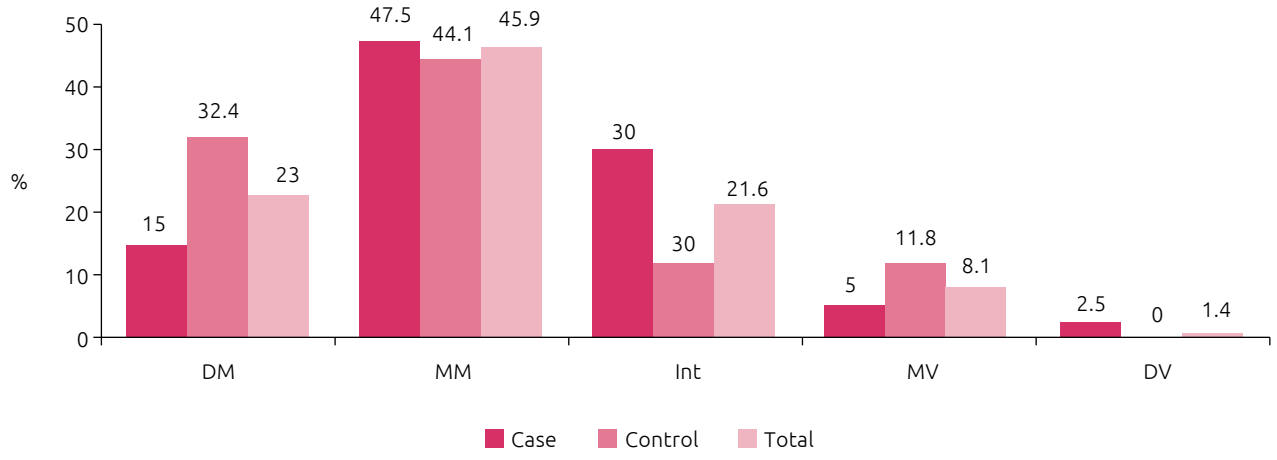
Likewise, the mean age of menopause was very similar, with 46.8 years in the controls and 47.7 in the cases and with maximum

Table 1. Characterization of the case and control groups to determine the medical, standard deviation (SD), extreme values and p-value.

Characteristic	Cases (n=40)				Controls (n=34)				p-value
	Average	SD	Minimum	Maximum	Average	SD	Minimum	Maximum	
Age (years)	54.1	13.2	33	79	48.6	12.2	21	70	0.070
Weight (Kg)	66.3	13.4	47	110	64.8	8.6	50	83	0.561
Height (m)	1.60	0.12	1.00	1.78	1.62	0.13	1.00	1.83	0.489
BMI (Kg/m^2)	26.22	6.09	19.38	47.00	25.31	6.97	17.63	60.00	0.552
Menarche (years)	13.0	2.0	10	17	13.5	1.7	11	18	0.242
Menopause (years)	47.7	6.8	30	58	46.8	4.2	38	53	0.654
First Pregnancy (years)	26.3	7.3	15	38	24.5	7.4	14	48	0.377
Children (n)	1.7	1.5	0	7	1.6	1.2	0	4	0.826

Table 2. Frequency relative and absolute of the variants stratified by study group and control.

Characteristic	Cases (n=40)		Controls (n=34)		Total (n=74)		p-value
	n	f(%)	n	f(%)	n	f(%)	
Contraceptive							
No	15	37.5	5	14.7	20	27.0	0.0527
Yes	25	62.5	29	85.3	54	73.0	
Hormone Replacement Therapy							
No	28	70.0	24	70.6	52	70.3	0.8415
Yes	12	30.0	10	29.4	22	29.7	
Difficulty Sleeping							
No	18	45.0	23	67.6	41	55.4	0.0857
Yes	22	55.0	11	32.4	33	44.6	
Use 1 hour before bedtime							
Nothing	3	7.5	3	8.8	6	8.1	0.1651
Television	22	55.0	11	32.4	33	44.6	
Cell phone and Computer	9	22.5	8	23.5	17	23.0	
TV + cell phone and Computer	6	15.0	12	35.3	18	24.3	
Environment sleeps							
Bright (with light)	2	5.0	2	5.9	4	5.4	0.9288
Penumbra	15	37.5	14	41.2	29	39.2	
Dark	23	57.5	18	52.9	41	55.4	
Family History of Cancer							
No	6	15.0	9	26.5	15	20.3	0.3508
Yes	34	85.0	25	73.5	59	79.7	
Family Breast Cancer							
No	28	70.0	20	58.8	48	64.9	0.4476
Yes	12	30.0	14	41.2	26	35.1	
Physical Activity							
No	22	55.0	14	41.2	36	48.6	0.3409
Yes	18	45.0	20	58.8	38	51.4	
Alcoholic Beverage							
No	35	87.5	28	82.4	63	85.1	0.7700
Yes	5	12.5	6	17.6	11	14.9	



DM: definitely matutine; MM: moderately matutine; Int: intermediate; MV: moderately vespertine; DV: definitely vespertine.

Figure 1. Chronotype profiles for the case, control and total groups.

age of 53 and 58, respectively. On the average of both variants (menarche and menopause), it is observed that the time of exposure to estrogen did not vary between the groups. That is, both cases of breast cancer as controls, were exposed to estrogen for a similar period of time.[12]

Concerning the age of first pregnancy, the groups had an average of 26.3 years in cancer patients and 24.5 years in controls, being the maximum 48 and 38 years, respectively. This data is relevant, since it is known that the development of first pregnancy is important for the maturation of breast cells to confer more protection from the action of carcinogens.[13] Due to the similarity of the average age, it was also not possible to consider this data as a risk factor. In a study with women in two cities in northeastern Brazil, it was observed that the age at last pregnancy represented a more significant risk for the disease than the age at first pregnancy.[13]

Regarding the use of contraceptives, in patients with breast cancer, 15 (37.5%) women said they never used, while in the control group 5 (14.7%) women said that. Among those who have confirmed the use of contraceptive, during all life period, accounted for 25 (62.5%) women in the case group and 29 (85.3%) in the control group (p=0.0527). Still in this study with 484 women, the authors showed that the age of diagnosis was significantly higher in patients who did not use contraceptive compared to those who did, despite the time of use, there wasn't a significant relationship with the age of breast cancer's diagnosis.[13]

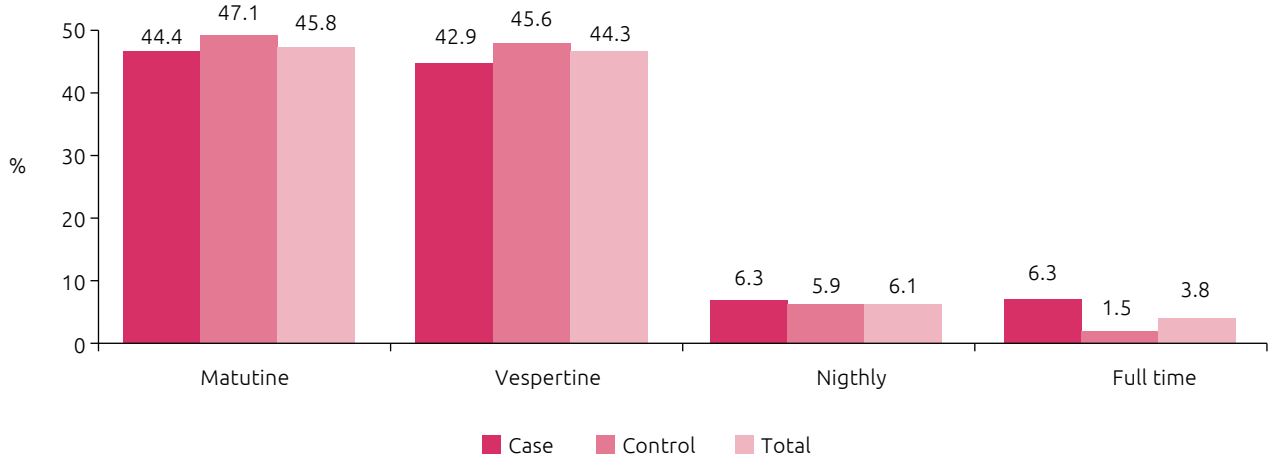


Figure 2. Work shifts for the case, control and total groups were divided into matutine, vespertine, nightly and full-time.

Table 3. Relative and absolute frequency of chronotypes and turns with their p-values.

Characteristic	Cases (n=40)		Controls (n=34)		Total (n=74)		p-value
	n	f(%)	n	f(%)	n	f(%)	
Chronotype							
Definitely Matutinal	6	15.0	11	32.4	17	23.0	0.1563
Moderately Matutinal	19	47.5	15	44.1	34	45.9	
Indifferent	12	30.0	4	11.8	16	21.6	
Moderately Vespertine	2	5.0	4	11.8	6	8.1	
Definitely Vespertine	1	2.5	0	0.0	1	1.4	
Shift							
Morning	28	44.4	32	47.1	60	45.8	0.5412
Afternoon	27	42.9	31	45.6	58	44.3	
Night	4	6.3	4	5.9	8	6.1	
Full time	4	6.3	1	1.5	5	3.8	
Total	63		68		131		
Chronotype × Shift							
Harmonic	11	17.5	5	7.4	16	12.2	0.0827
Disharmonic	19	30.2	29	42.6	48	36.6	

On the use of hormone replacement therapy (HRT), 30% (20) of patients with breast cancer made use of this therapy, while 70% (28) did not; at the controls, 70.6% (24) did not use and 29.4% (10) did. According to the Collaborative Group on Hormonal Factors in Breast Cancer, the use of hormone replacement therapy was related to increased breast cancer, and the risk also increased with continuous hormone therapy. In a second study, both the use of estrogen alone and combined with progesterone also showed an increased risk of developing breast cancer.[13] But in another study, 78.9% of patients with breast cancer, studied for this variant, did not use HRT, which is similar to the findings of this research.[13]

The desynchronization of circadian cycle is seen in some longitudinal studies as a major risk factor for developing breast cancer. Besides Nurses' Health Study, another study with flight attendants working at discordant times of their circadian rhythm, found that this enables the development of breast cancer.[10] Another several international studies in blind women showed a lower incidence of cancers, including breast cancer. It's justified because they have little or none exposure to light at night and thereby they wouldn't have reduced levels of melatonin.[7]

One of the theories that justify this association is the suppression of melatonin production. This hormone, produced by the pineal gland and suppressed by light, plays a central role in the synchronization process of circadian rhythms.[14] In addition to its action and influence of the secretion of hormones (such as estrogen)[8] there is also the oncostatic action to alter the cell cycle by inhibiting mitosis, partially delaying metaphase, and also strengthening the immune system, removing free radicals and stimulated expression of the tumor suppressor gene, such as p53.[8]

Table 4. Cases of patients undergoing chemotherapy.

Characteristic	Cases (n=28)	
	n	f(%)
Chemotherapy		
No	8	20.0
Yes	28	70.0
Not Available	4	10.0
Best period for chemotherapy		
Morning	14	50.0
Evening	4	14.3
Indifferent	10	35.7
Best Chemotherapy × Chronotype		
Definitely Matutinal	4	14.3
Moderately Matutinal	15	53.6
Indifferent	7	25.0
Moderately Vespertine	1	3.6
Definitely Vespertine	1	3.6
Worst Period Collateral Effects		
Morning	4	14.3
Evening	4	14.3
Night	3	10.7
Indifferent	17	60.7

From the collected data, it was possible to assess that among all cases, 6.3% worked both night shifts or full-time, whereas in the control this value was 5.9 and 1.5%. From the patients with breast cancer, 44.4% worked in the morning and 42.9% in the evening. Furthermore, when asked about the environment in which they slept, 5% of the cancer patients slept in a lighting room; 37.5% slept in penumbra and 57.5% in the dark. At the controls, 5.9% sleep with light; 41.2% in penumbra and 52.9% in the dark. These data are relevant because both work in the night and sleep in bright environments, where there is the inhibitory action of light on the release of melatonin.

Another important factor is the suppression of sleep, causing changes in the regulation and in biological clock genes' activity. In a study that evaluated 17 men in two sessions (in one of them, patients slept the night and in the other they stayed awake), the authors were able to demonstrate, through samples collected at these two moments, that epigenetic mechanisms caused chemical changes in the DNA molecule, which regulates how genes are activated or inactivated.[15] These changes, observed in night shift workers and even in patients with type 2 diabetes, could lead to changes in the genome of the tissues and affect the metabolism for longer periods.

From the patients analyzed, 55% patients with breast cancer and 32.4% of controls had some type of difficulty in sleeping. Based on the study above, it may be necessary to collect samples to highlight the possible chemical changes in these patients' DNA molecule.

Another data analyzed was the relationship between chronotype and shift work in patients with breast cancer and controls. The fact that someone prefers to perform their activities in a given period, as the morning, for example, is nothing more than an endogenous interindividual component that is essential for the biological clock. Relying on diurnal preference, it is possible to set different types of chronotypes, ranging from matutinal, vespertine, until intermediary.[3] By χ^2, the characteristics between case and control groups were similar, so it wasn't possible to confirm the relationship between working out of chronotype's best time and breast cancer.

In this study, 28 (70.0%) patients did chemotherapy. Referring which period they felt better doing chemotherapy, 50.0% showed preference to the morning shift, while 35.7% said they were indifferent. When the preferred period for the completion of chemotherapy was contrasted with chronotype, it was noticed that most of the patients (53.6%) were within the chronotype "moderate matutinal" and, from these, 46.7% used chemotherapy in the morning.

Regarding the time that most felt the impact of collateral effects of chemotherapy, the majority (60.7%) declared indifferent. When the most critical period for the collateral effects of chemotherapy was contrasted with chronotype, it was noticed that 80.0% of patients had desynchronization. This desynchronization is due to perform chemotherapy in times of the day that doesn't match their chronotypes. It is known that the occurrence of adverse effects due to patient's intolerance to medication, considering the time of the day that they are administered.[16]

Understanding this, it is possible to administer the cytostatic maximizing its actions, simultaneously increasing the effectiveness of the treatment and reducing collateral effects.[2]

CONCLUSION

This study could not correlate the oncogenesis of breast cancers and labor activity occurring in a different shift of the individual's chronotype. This subject still needs further studies.

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