CRIMSON PUBLISHERS
Wings to the Research

Gerontology & Geriatrics Studies

ISSN 2578-0093

Review Article

Changes in Melatonin Biorhythms and Immune-Neuroendocrine Interactions in Oncological Patients of Different Ages

Labunets Irina F*

Cell and Tissue Technologies Department, Experimental Modeling Laboratory, Ukraine

***Corresponding author:** Irina Labunets, Experimental Modeling Laboratory, Cell and Tissue Technologies Department, Institute of Genetic and Regenerative Medicine National Academy of Medical Sciences of Ukraine, Vyshgorodskaya Street 67, PO Box: 04114, Kiev, Ukraine, Tel: 80444687550; Fax: 38044 4687541; Email: irina_labunets@ukr.net

Submission: January 18, 2018; **Published:** April 27, 2018

Abstract

The frequency of tumors in aging increases worldwide. The use of chronobiological approaches in studying circadian and circannul rhythms of various organism functions may be perspective for effective diagnosis, prevention and treatment of oncologic patients of different age. This review presents the data about changes of the basic components in control system of the biorhythms in aging and tumor development. We present the results of our study about the biorhythms of the immune system in healthy adult subjects and their changes in aging and cancer as well as their links with the disturbances in rhythmicity of thymic hormone thymulin. The role of disturbances in the interrelations of biorhythms melatonin and cortisol levels for development of desynchronosis thymulin and immune system functions in aging and cancer are underlined.

The importance of using chronobiological approaches for estimation of changes in the immune and neuroendocrine system in the oncopatients and the use of melatonin as synchronizing agent in the their basic treatment schemes is substantiated. Schemes of melatonin administration should be based on age-related changes of the sensitivity immune and endocrine systems to its influence.

Keywords: Biorhythms; Melatonin; Thymulin; Cortisol; Immune system; Age; Oncological patients

Introduction

Time-dependent rhythmicity in the organization of physiological processes is an important property of the living organisms [1,2]. Circadian (daily) and circannual (seasonal) rhythms play the main role in human organism adaptation to the changing external factors (light, temperature, geomagnetic field and humidity). Among such factors the photoperiod has the most stable synchronizing properties for circadian and circannual rhythms [3,4]. In aging there occur disturbances in many organism systems, in particular in the neuroendocrine and immune systems, which associated with development of different forms of tumors [5-8]. The disturbances in the rhythmicity of these system functions, in their turn, may be linked with changes in melatonin-forming function of the pineal gland in aging and tumor development [8-10].

This article presents the review of the results obtained by other investigators and own data about the role of changes in the circadian and circannual biorhythms of melatonin for desynchronization of immune-neuroendocrine interactions in the oncologic patients of different ages.

Regulation of Biorhythms in Healthy and Tumor Organism

Adult subjects

The control system of these rhythms includes such components as

A. generator (pacemaker) of endogenic rhythms of organism functions-suprachiasmatic nucleus (SCN) of the hypothalamus,

B. afferent way to pacemaker, and

C. efferent pathway from the pacemaker to the peripheral organs [1,11].

SCN of the hypothalamus receives information about the external illumination through the retinohypothalamic tract [12,13]. As a result, the activity and expression of circadian clock genes (Per1, Per2, Per3, Cry1, Cry2, Clock, Bmall/Mop3, Tim, etc) in SCN undergo changes. The transformed signals from SCN of the hypothalamus arrive in the limbic brain, peripheral endocrine gland.

Numerous studies have stressed that the pineal gland and its hormone melatonin plays a key role in regulation of human circadian and circannual rhythms [9,14]. In adult subjects melatonin production during dark period and with shortening season photoperiod raises. Melatonin coordinates endogenic rhythms that are generated in SCN, influencing through the own receptors, density and affinity of which increasing in the dark period [4,15]. Also it was shown the link melatonin with peripheral clocks in peripheral tissues of the body [13].

Aging subjects

There are age-dependent disturbances in the circadian and circannual rhythms of melatonin production by the pineal gland. The nocturnal peak of blood melatonin was lower in elderly human subjects compared to adult person [9,16-18]. We showed the decreasing winter melatonin peak or its shifting to the spring in elderly people [18,19]. The structure and functioning of SCN of the hypothalamus destroy in aging [19]. Literature data have shown the importance of dysfunction circadian clock genes in SCN of hypothalamus (Bmall1, Clock, Per2) in aging and age-related pathologies [20]. The positive effect of exogenous melatonin in restoring age-dependent alterations of such genes have also been documented [19].

Tumor organism

Circadian disturbances has been found in majority oncopatients and in 50% of patients with metastatic tumors [21]. Disturbances of interrelations between pineal gland and SCN of the hypothalamus in tumor development can be linked with their morphofunctional changes [10,22,23]. Thus, decreasing in melatonin blood level is caused by falling of its synthesis in pineal gland, amount of pineal β-adrenoreceptors and/or their sensitivity to stimulation of noradrenaline, and changes of hormone metabolism. The suppression of melatonin-forming function of pineal gland accelerates development of tumours, whereas its increasing or administration of melatonin influence the opposite manner [6,10]. Melatonin synchronizes the amplitude and phase of rhythms of some functions in animals with tumors. Such changes are accompanied with increased longevity, reduced tumor weight and antimetastatic action [24]. The possible involvement of circadian clock genes in SCN (Per1, Per2, Cry1, Bmal1, Tim) in the development of different forms of cancer in humans was described in the review of Savvis and co-workers [5].

The disturbances of melatonin control of expression clock genes in the peripheral tissues can also promote tumor growth [25]. So, mice with mutation of gene Per2 are more inclined to spontaneous tumorigenesis. Lower expression of the Per gene group leads to the uncontrollable proliferation of cells and DNA damage and enhanced apoptosis. Summing up, the results of disturbances in functioning of the basic parts of control system of biorhythms can be desynchronization of the functions organs and systems in tumor development.

Biorhythms of the Thymus and Immune System in the Healthy and Oncopatients

Healthy subjects

The literature data and our own findings revealed the circadian and circannual rhythms of blood amount T-, B-lymphocytes, granulocytes, and immunoglobulin (Ig) and cytokine levels in adult human subjects [8,26-29]. Immune system functions are under control of thymic hormones, in particular thymulin [30-32]. Age-dependent decrease of blood thymulin level precede immune system disturbances in aging [33]. Other authors and ourselves found night time peak of blood thymulin level in adult human subjects [17,34]. We revealed season fluctuations in the thymulin level in adult healthy subjects and their disturbances in aging [18,35]. It is characteristic of elderly human subjects that age changes of the rhythmicity of immune system functions coincide with desynchronosis of the thymic endocrine function [8,18,27].

Oncologic patients

According to the published data, the circadian rhythms of blood lymphocytes and their T-populations are destroyed in tumor organism, and seasonal variations in tumor growth are connected with the seasonal disturbances of immune system functions [36]. We have established the relationship between thymus and immune system functioning desynchronosis in the oncologic patients [8]. Further, we have establied in patients with cancer of esophagus and cardia (CEC) at the aged 50-73 years the conjugation/associativity of disturbances of circadian rhythm of thymulin, on the one hand, and changed rhythmicity of the blood amount of T-lymphocytes and IgG, on the other [37], In particular, we did not observe increase of nocturnal amount of blood T-lymphocytes and decrease of blood IgG level in the patients with monotonous rhythm of thymulin level.

Disturbances of circannual fluctuations of thymulin level in oncologic patients aged 20-40 years versus healthy people were characterized by the monotony (skin melanoma, breast cancer) or displacement of the seasonal acrophase (uterus chorioncarcinoma) and the decrease of thymulin level during some seasons. It appeared that circannual fluctuations of amount blood T-lymphocytes in the oncologic patients correlate with thymulin level. We may stress that changes in seasonal fluctuations of blood T-lymphocyte amount are registered already at the pretumoral stage of disease [8]. In the comparison with healthy individuals, the oncologic patients displayed disorders of seasonal sensitivity of T-lymphocytes to the influences of thymic hormones. In addition, the amount of blood T-suppressors either did not change during a year or their seasonal acrophase became more intensive. In the oncologic patients we observed monotony of seasonal fluctuations in the amount of blood B-lymphocytes, displacement their seasonal acrophase or inversion of the rhythm. Beside, in patients, unlike healthy people, the steady tendency to decrease of the IgG level in winter and monotony season fluctuations in the interferon (IF) and interleukin (IL)-1β levels is marked [38].

We may conclude that in all groups of oncopatients there are signs of intrasystemic desynchronosis, taking place between indices of peripheral immune system, on the one side, and the study indices and the thymic hormone, on the other side. According to published data, the thymic hormones/thymulin influence on such rhythmic processes in immune system as migration, proliferation and differentiation of lymphocytes [30-32]. Based on our data, there is a relationship between fluctuations of blood thymulin level and amount of T-lymphocytes in oncologic patients. Moreover, the synchronic rhythmicity of thymic hormone production and sensitivity T-lymphocytes to their influence are essential for effective hormonal action on the T-lymphocytes. In our study the disturbances of relationships between the rhythm of blood thymulin level and seasonal sensitivity of T-lymphocytes to its influence were revealed in the oncologic patients [8].

Changes of the rhythm in the IF level and its antitumor properties are well studied [39]. The thymic hormones are capable to increase interferonogenesis at tumoral processes. Therefore we believe that thymulin and IF level desynchronization in the on copatients are interrelated [38]. The effects of thymic hormones on B-lymphocytes differentiation in the bone marrow and their ability to restore the diminishing blood level of Ig in the people with an immunodeficiency have demonstrated [33]. In our experiments the thymic hormones restore disturbed circannual rhythms of Ig production that can be connected with their influence via the rhythm of the T-suppressors [40]. We did observe an intensive seasonal amplitudes of the amount of blood T-suppressors in the oncologic patients. As has been stressed by other researchers, both decrease and increase of the amplitude of the rhythms are connected with reduced organism adaptation [2].

Thus, disturbances of the biorhythms in blood thymulin level in patients with tumor of various genesis can be the important pathogenetic factors in changes of immune system rhythmicity. In turn, desynchronosis of thymic endocrine function in oncopatients can be connected with disturbances of its relationship with functioning of other endocrine glands, in particular pineal gland and adrenal gland cortex.

The Dysfunction of Pineal Gland and Adrenal Gland and the Immune System Desynchronosis in the Oncopatients

Biorhythms of melatonin and cortisol in the oncologic patients

According to the published data, the nocturnal peak of melatonin blood level is decreased in the oncologic patients (breast cancer, cancer of thyroid gland, lungs and prostate) [10]. The intensity of decrease of melatonin level correlates with the stage, biological properties of tumor and its localization. The pineal gland influences on the functioning of the hypothalamus-pituitary-adrenal axis that is important for the development of adaptive reactions in the organism [41,42]. Hypercorticism in the oncopatients correlates with disease progression, appearance of recidives and metastases [43]. The monotony of circadian rhythms of the blood cortisol level in such patients versus young healthy people was monotonic [42].

We not only have established the disturbances of circadian and circannual rhythms of melatonin and cortisol blood level in oncological patients, but also their link [37,38]. In our data, in young healthy people (20-30 years) melatonin level increases in the evening and especially at night, whereas at healthy people more 50 years the difference between its day and night values decreases to 2times ($p < 0.05$) [17]. At the majority of patients with CEC circadian rhythm of melatonin blood level was monotony or inverted [37]. In a part of patients, despite of increasing melatonin level at night, its values were lesser versus age control.

In case of monotony or inversion of melatonin circadian rhythm the scope of daily fluctuations of blood cortisol level was considerably above (18times), than in patients with activation of pineal gland function in the evening (8times) and in age control group (3times). Such changes in cortisol level may be a result of development of chronic stress in oncologic patients [37,44]. According to our data, in the healthy individuals there is a winter peak of the blood melatonin level [18]. In the oncologic patients the melatonin level decreases and its seasonal fluctuations are monotonic [18,38,45]. Beside, in them the seasonal hormone acrophase displaces in the spring. Disturbances of the circannual rhythms of the levels of melatonin and cortisol were interrelated [46].

Immunnoendocrine interrelations in the Oncopatients

One of the mechanisms of oncostatic melatonin effect is connected with its immunomodulatory action (normalization of zinc balance, thymulin level and hematopoesis activation [6,47]. According to our data, an elevated level of melatonin in the animals with malignancies inhibited tumor growth and simultaneously activated thymic endocrine function [48]. According to DP Cardinali et al. [49], thymus is the primary target organ for melatonin action. In the oncologic patients, activation of thymic endocrine function at night time is observed in the case of increased melatonin level during this period. In case of the monotony or inversion of the circadian rhythm of melatonin the fluctuations of thymulin were monotonic.

Melatonin is capable to influence directly synthesis and secretion of hormones by thymus [40,49,50]. The effect of melatonin on the thymic endocrine function can pass through the changes of hypothalamus-pituitary-adrenal axis functioning [41,51,52]. High concentrations of the glucocorticoid suppress thymic endocrine function [40,52]. The efficiency of thymic hormones administration is increased under condition of short-term hypocorticism. Fluctuations of the expression and/or sensitivity of the glucocorticoid receptors on the thymic epithelial cells are controlled by the melatonin [50]. Dronka and co-workers stressed, that investigations of the neuro-endocrine-immune relationships in cancer will help to substantiate new therapeutic approaches to cancer treatment [53].

It is known that the frequency of tumors increases every 5years in the people after 40 years of age [43]. Therefore our observation over the oncopatients aged between 20 and 40 years has shown that rhythmicity of the immunoendocrine relations resembled the rhythmicity of healthy old individuals [18,37,38,54].

How to cite this article: Labunets I F. Changes in Melatonin Biorhythms and Immune-Neuroendocrine Interactions in Oncological Patients of Different Ages. Gerontol & Geriatric Stud .3(2). GGS.000557.2018. DOI: 10.31031/GGS.2018.03.000557

In the spring the seasonal peak of melatonin blood level is high in patients younger 40 years. The rhythm of thymulin and cortisol levels becomes monotonous and the amount of T-lymphocytes is the highest in the spring. These data evidence for the possible acceleration of age-associated changes of the circannual rhythm of the pineal gland, thymus, adrenal cortex and immune system in the oncopatients. Our results about the changes of seasonal reaction of the T-lymphocytes on regulatory influence by thymic hormone in the oncologic patients younger 40 years also confirm such possibility.

Perspectives and Conclusion

Chronobiological investigations of the immunoendocrine interactions in the oncologic patients are important from the following viewpoints:

A. Estimation of biorhythms of immune and endocrine system functions may be useful for diagnosis, substantiation of risk factors and the criteria of the prognosis of tumor development, and appearance of recidives and metastasis after basic treatment. As has been shown by some authors, the earliest disturbances of organism functions at pathological conditions are linked with their biorhythms and are registered before the appearance of clinical signs of disease [2].

B. To improve methodological approaches to an objective estimation of the dysfunction of the immune and endocrine systems in oncopatients, it is essential to study circadian and circannual rhythms of the above systems.

C. Effects of the immunomodulatory agents in oncologic patients should be estimated with an account of the seasons.

D. With the account of circadian and circannual rhythms of the proliferative activity of the lymphocytes and bone marrow cells [2,40,53], the sensitivity of the latter to damaging action of chemo-, radio- and hormone therapy varies allowing to personalize treatment regiments of oncology patients.

E. Melatonin, as pharmacological agent, can be useful to restore desturbed rhythms of the immune and endocrine system functions at tumoral process. It influences the phase and amplitude of rhythms, regulates fluctuations of the glucocorticoid receptor expression on the lymphocytes, realizes own synchronizing influence on immune system through thymulin and adrenal glands [22,40,49,55]. Melatonin as synchronizing agent may be applied independently or in a combination with basic methods of oncopatients treatment. Melatonin can be useful in oncology practice in a combination with thymic preparation in adjuvant regiment.

F. As the patern of rhythmicity of immune and endocrine systems in oncopatients remind that in healthy elderly people, schemes of melatonin administration should be based on age-related changes of these system sensitivity to its influence [8,17,40]. Thus, the use of melatonin in basic treatment oncopatients under the optimized schemes can essentially raise its efficiency.

References

1. Reinberg A, Ashkenazi I (2003) Concepts in human biological rhythms. Dialogues Clin Neurosci 5(4): 327-342.
2. Komarov FI, Rapoport SI (2000) Chronobiology and chronomedicina. Moscow, Triada, India.
3. Duffy J F, Wright KP (2005) Entrainment of the human circadian system by light. J Biol Rhythms 20(4): 326-338.
4. Bonmati Carrion MA, Arguelles Prieto R, Martinez Madrid MJ, Reiter R, Hardeland R, et al. (2014) Protecting the melatonin rhythm through circadian healthy light exposure. Int J Mol Sci 15(12): 23448-23500.
5. Savvidis C, Koutsilieris M (2012) Circadian rhythm disruption in cancer biology. Mol med 18: 1249-1260.
6. Anisimov VN, Vinogradova IA, Panchenko AV, Popovich IG, Zabezhinski MA (2012) Light-at-night-induced circadian disruption, cancer and aging. Curr Aging Sci 5(3): 170-177.
7. Mate I, Madrid JA, De la Fuerite M (2014) Chronobiology of the neuroimmunoendocrine system and aging. Curr Pharm Des 20(29): 4642-4655.
8. Labunets IF, Grinevich YuA (2014) Biological rhythms of immune system functions and possibilities of their regulation in patients with malignant tumours (review of published and authors' own research data). Clin Oncol 2(14): 46-52.
9. Touitou Y (2001) Human aging and melatonin. Clinical relevance. Exp Gerontol 36(7): 1083-1100.
10. Bartsch Ch, Bartsch H, Peschke E (2009) Light, melatonin and cancer: current results and future perspectives. Biol Rhythm Res 40(1): 17-35.
11. Erren T C, Reiter RJ (2009) Defining chronodisruption. J Pineal Res 46(3): 245-247.
12. Maywood ES, O Neill JS, Chesham JE, Hastings MH (2007) Mini Review: The circadian clockwork of the suprachiasmatic nuclei-analysis of a cellular oscillator that drives endocrine rhythms. Endocrinology 148(12): 5624-5634.
13. Ozturk N, Ozturk D, Kavakli IH, Okyar A (2017) Molecular aspects of circadian pharmacology and relevance for cancer chronotherapy. Int J Mol Sci 18(10): E2168.
14. Reiter RJ, Rosales Corral S, Coto Montes A, Boga JA, Tan DX, et al. (2011) The photoperiod, circadian regulation and chronodisruption : requisite interplay between the suprachiasmatic nuclei and the pineal and gut melatonin. J Physiol Pharmacol 62(3): 269-274.
15. Dubocovich ML (2007) Melatonin receptors: Role on sleep and circadian rhythm regulation. Sleep Med 8(Suppl 3): 34-42.
16. Korkushko OV, Khavinson VKh, Shatilo VB (2006) Pineal gland: ways for correction in aging. Nauka, St Petersburg, Russia.
17. Labunets IF (2005) Melatonin influence on rhythms of thymus, immune system and adrenal cortex functions in old persons. Probl Aging Longevity 14(4): 313-322.
18. Labunets IF (2013) Sex peculiarities of age-related changes in circannual rhythms of pineal gland, hypothalamo-pituitary-adrenal axis and thymus in healthy subjects. Adv Gerontol 3(4): 290-296.
19. Jenwitheesuk A, Nopparat C, Mukda S, Wongchitrat P, Govitrapong P (2014) Melatonin regulates aging and neurodegeneration through energy metabolism, epigenetics, autophagy and circadian rhythm pathways. Int J Mol Sci 15(9): 16848-16884.
20. Solovyev IA, Dobrovolskaya EV, Moskalev AA (2016) Genetic Control of Circadian Rhythms and Aging. Genetika 52(4): 393-412.

21. Innominato PF, Roche VP, Palesh OG, Ulusakarya A, Spiegel D, et al. (2014) The circadian timing system in clinical oncology. Ann Med 46(4): 191-207.

22. Blask DE (2009) Melatonin, sleep disturbance and cancer risk. Sleep Med Rev 13(4): 257-264.

23. Klerman EB (2005) Clinical aspects of human circadian rhythms. J Biol Rhythms 20(4): 375-386.

24. Otalora BB, Madrid JA, Alvarez N, Vicente V, Roi MA (2008) Effects of exogenous melatonin and circadian synchronization on tumor progression in melanoma-bearing C57Bl6 mice. J Pineal Res 44(3): 307-315.

25. Stevens RG (2005) Circadian disruption and breast cancer. From melatonin to clock genes. Epidemiology 16(2): 254-258.

26. Logan RW, Sarkar DK (2012) Circadian nature of immune function. Mol Cell Endocrinol 349(1): 82-90.

27. Labunets I (2015) Immune-neuroendocrine interactions involving thymus and pineal gland in stem cell therapy of age-related diseases. Immunology, Endocrine & Metabolic Agents in Medicinal Chemistry (IEMAMC) 15(2): 101-120.

28. Scheirmann Ch, Kunisaki Y, Frenette PS (2013) Circadian control of the immune system. Nat Rev Immunol 13(3): 190-198.

29. Geiger SS, Fagundes CT, Siegel RM (2015) Chrono-immunology:progress and challenges in understanding links between the circadian and immune systems. Immunology 146(3): 349-358.

30. Csaba G (2016) The immunoendocrine thymus as a pacemaker of lifespan. Acta Microbiol Immunol Hung 63(2): 139-158.

31. Reggiani PC, Schwerdt Ji, Console GM, Roggero EA, Dardenne M, et al. (2014) Physiology and therapeutic potential of the thymic peptide thymulin. Curr Pharm Des 20(29): 4690-4696.

32. Bach JF, Bach MA, Blanot D, Ericas E, Charreire J, et al. (1978) Thymic serum factor (FTS). Bull Inst Pasteur 76: 325-398.

33. Hirokawa K, Utsuyama M, Makinodan T (2006) Immunity and aging. Principles and Practice of Geriatric Medicine. In: Pathy MS (Ed.), J Wiley 2: 19-37.

34. Molinero P, Soutto M, Benot S, Hmadcha A, Guerrero JM (2000) Melatonin is responsible for nocturnal increase observed in serum and thymus of thymosin alpha1 and thymulin concentrations: observations in rats and humans. J Neuroimmunol 103(2): 180-188.

35. Labunets IF (2017) Age-related changes in the melatonin and thymulin biorhythms as risk factors for human neurodegenerative diseases. Gerontol & Geriatric Stud 1(2): 1-5.

36. Nelson R J, Blom JMC (1994) Photoperiodic effects on tumor development and immune function. J Biol Rhythms 9(3-4): 233-249.

37. Labunets IF, Grinevich YuA, Kirkilevsky SI, Yugrinova LG, Lukashenko AV (2007) Circadian rhythm of pinealgland melatonin-producing function in malignancies: relationship with the rhythmic activity of thymus and adrenal cortex. Oncology 19(1): 17-20.

38. Labunets IF, Grinevich YuA (2004) The peculiarities of rhythmical fluctuations immunological indices in tumor deseases. Oncology 6(1): 16-22.

39. Petrovsky N, Harrison LC (1998) The chronobiology of human cytokine production. Int Rev Immunol 16(5-6): 635-649.

40. Labunets I (2012) Pineal gland and rhythms of immune system in aging. Experimental study. LAP LAMBERT Acad Publ: Saarbrucken, Germany.

41. Dickmeis Th (2009) Glucocorticoids and the circadian clock. J Endocrinol 200(1): 3-22.

42. Ferrari E, Arcaini A, Gornati R, Pelanconi L, Cravello L, et al. (2000) Pineal and pituitary-adrenocortical function in physiological aging and in senile dementia. Exp Gerontol 35(9-10): 1239-1250.

43. Hormones (2005) age and cancer. In: Berstein LM (Ed.), Nauka, St Peterburg, Russia.

44. Gomaa A MS, Galal HM, Abou Elgait AT (2017) Neuroprotective effects of melatonin administration against chronic immobilization stress in rats. Int J Physiol Pathophysiol Pharmacol 9(2): 16-27.

45. Grinevich Yu A, Labunets IF (1986) Melatonin, thymic serum factor, and cortisol levels in healthy subjects of different age and patients with skin melanoma. J Pineal Res 3(3): 263-275.

46. Labunets IF (1996) Age-related biorhythmical disfunction of the pineal gland, thymus and hypophysial-adrenal system in healthy subjects. Aging Immunol Infect Dis 6(3-4): 167-176.

47. Mocchegiani E, Perissin L, Santarelli L, Tibaldi A, Zorzet S, et al. (1999) Melatonin administration in tumor-bearing mice (intact and pinealectomized) in relation to stress, zinc, thymulin and IL-2. Int J Immunopharmacol 21(1): 27-46.

48. Anisimov VN, Zhukova OV, Labunets IF, Bartsch H, Bartsch C (1995) The inhibitory effect of light deprivation on N-nitrozomethylurea-induced carcinogenesis and on the growth of transplantated tumors in rodents: possible involvement of the pineal gland and the immune system. Exp Oncology 17(1): 47-54.

49. Cardinali DP, Esquifino AI, Srinivasan V, Pandi Perumal SR (2008) Melatonin and the immune system in aging. Neuroimmunomodulation 15(4-6): 272-278.

50. Saintz RM, Mayo JC, Reiter RJ, Antolin I, Esteban MM, et al. (1999) Melatonin regulates glucocorticoid receptor: an answer to its antiapoptotic action in thymus. FASEB J 13(12): 1547-1556.

51. Reggiani C, Morel GR, Console GM, Barbeito CG, Rodriguez SS, et al. (2009) Thymus-neuroendocrine axis. Physiology, molecular biology, and therapeutic potential of the thymic peptide thymulin. Ann N Y Acad Sci 1153(1): 98-106.

52. Savino W, Mendes da Cruz DA, Lepletier A, Dardenne M (2016) Hormonal control of T cell development in health and disease. Nat Rev Endocrinol 12(2): 77-89.

53. Dronca RS, Markovic SN, Holtan ShG, Porrata LF (2011) Neuro-endocrine-immune crosstalk and implications for cancer therapy. J Cell Sci Ther 2(2): 1000102e.

54. Labunets I F, Grinevich YuA (2003) Activity of the pineal gland, thymus and hipophisial-adrenal system in oncological patients. Exp Oncol 25(2): 138-142.

55. Kubatka P, Zubor P, Busselberg D, Kwon TK, Adamek M, et al. (2018) Melatonin and breast cancer: Evidences from preclinical and human studies. Critical Reviews in Oncology/Hematology 122: 133-143.

How to cite this article: Labunets I F. Changes in Melatonin Biorhythms and Immune-Neuroendocrine Interactions in Oncological Patients of Different Ages. Gerontol & Geriatric Stud .3(2). GGS.000557.2018. DOI: 10.31031/GGS.2018.03.000557