Neuroendocrinology Letters ISSN 0172–780X

ORIGINAL ARTICLE

Serum melatonin circadian profile in women suffering from the genital tract cancers

Michal Karasek,[1] Andrzej J. Kowalski[2] & Krystyna Zylinska[3]

1. Laboratory of Electron Microscopy, Chair of Pathomorphology, Medical University of Lódz, Lódz, Poland.
2. Institute of Gynecology and Obstetrics, Medical University of Lódz, Lódz, Poland.
3. Department of Experimental Endocrinology and Hormone Diagnostics, Institute of Endocrinology, Medical University of Lódz, Lódz, Poland.

Correspondence to: Prof. Dr. Michal Karasek, Laboratory of Electron Microscopy, Chair of Pathomorphology, Medical University of Lódz, Czechoslowacka 8/10, 92-216 Lodz, Poland.
TEL/FAX: +48 42 675 7613
E-MAIL: karasek@psk2.am.lodz.pl

Submitted: *December 15 1999*
Accepted: *January 24, 2000*

Key words: **melatonin, pineal gland, cancer, malignant tumors, female genital tract, endometrial cancer, invasive ovarian cancer, squamous cervical cancer, circadian rhythms**

*Neuroendocrinology Letters 2000; **21**:109–113 pii: NEL210200A01 Copyright © Neuroendocrinology Letters 2000*

Abstract

OBJECTIVES: Although there is increasing evidence that the pineal gland may play a role in human malignancy, the studies on melatonin concentrations in different types of malignant tumors brought about controversial results. However, changes in melatonin concentrations have been observed in some types of human malignant tumors. Therefore we decided to study the circadian melatonin rhythm in patients suffering from malignant tumors of the female genital tract, and to compare them with subjects free from neoplastic disease (healthy volunteers and patients with myomatous uterus). MATERIAL AND METHODS: A total of 46 women were analyzed in this study. The subjects were divided into 3 groups. The first group consisted of 23 patients with malignant tumors of the genital tract (mean age 50.3±2.2 years; mean±SEM, range 32–77 years). The second group consisted of 16 healthy volunteers (mean age 50.9±1.8 years; mean±SEM, range 42–63) who served as the first control group, whereas the third group consisted of 7 subjects who suffered from myomatous uterus (mean age 45.7±2.3 years; mean±SEM, range 39–56) and served as the second control group without malignancy. Blood samples were collected at 08:00, 12:00, 16:00, 20:00, 22:00, 24:00, 02:00, 04:00, 06:00 and 08:00 h. Melatonin concentration was measured using RIA kit. RESULTS: There were no significant differences in circadian melatonin profiles among the three groups studied. Taking into consideration the type of tumor of the genital tract, significantly lower melatonin secretion has been found in patients with endometrial cancer in comparison with tumor-free control groups, whereas no significant differences in melatonin secretion have been observed between tumor-free control groups and patients with invasive ovarian cancer and squamous cervical cancer. However, significant differences have been observed between endometrial cancer and invasive ovarian cancer. CONCLUSION: Its seems probable that melatonin concentrations in human malignancy may, at least partly, depend on hormone dependency of the particular type of tumor.

Introduction

The relationship between the pineal gland (especially its hormone melatonin) and neoplastic disease is well documented in the animal model [see 1–5]. Although there is increasing evidence that the pineal gland may also play a role in human malignancy, the studies on melatonin concentrations in different types of malignant tumors brought about controversial results. Low, high, and normal melatonin concentrations have been reported in various types of human malignant disease [see 2, 6]. It should be stressed, however, that numerous earlier studies based on measurements of melatonin concentrations in one time-point only, during the daytime, and therefore these studies are of limited value. In recent years circadian melatonin profiles have been estimated in some types of human neoplasms. Depressed nighttime melatonin levels have been observed in primary breast cancer [7–9], prostate cancer [10, 11], colorectal carcinoma [12], and in uterine corpus adenocarcinoma [13]. Moreover, melatonin has been shown to inhibit development and/or growth of various experimental animal tumors [1–5], and some human cell lines in vitro (MCF-7 breast cancer [14, 15], Jurkat T-lymphoma [16], JAr choriocarcinoma [17], M-6 melanoma [18], SK-N-SH neuroblastoma [19], uveal melanoma [20] and LNCaP prostate tumor [21]), also those originated from female genital tract (JA-1, SK-OV-3, BG-1 ovarian cancer [22–24] and ME-180 human cervical cancer [25]).

Therefore we decided to study the circadian melatonin rhythm in patients suffering from various malignant tumors of the female genital tract, and to compare them with subjects free from neoplastic disease (healthy volunteers and patients with myomatous uterus).

Material and methods

A total of 46 women were analyzed in this study. The subjects were divided into three groups. The first group consisted of 23 patients with malignant tumors of the reproductive system (mean age 50.3±2.2 years; mean±SEM, range 32–77 years). Among the subjects of the first group 8 patients (mean age 50.5±5.4 years; mean±SEM, range 32–77) suffered from invasive ovarian cancer, 6 patients (mean age–46.8±3.5 years; mean±SEM, range 37–57) suffered from squamous cervical cancer, 7 patients (mean age 51.3±2.4 years; mean±SEM, range 41–59) suffered from endometrial cancer, and 2 patients (45 and 61 years old) suffered from the vulval cancer. The diagnosis in the patients of the first group was confirmed by postoperative histopathological examination. The second group consisted of 16 healthy volunteers (mean age 50.9±1.8 years; mean±SEM, range 42–63) who served as the first control group, whereas the third group consisted of 7 subjects who suffered from myomatous uterus (mean age 45.7±2.3 years; mean±SEM, range 39–56) and served as the second control group without malignancy.

Patients were admitted to the hospital at least 48 hours before the study. One day before and during blood sampling the period of darkness in patients' room lasted from 21:00 to 07:00 h. Blood samples were collected at 08:00, 12:00, 16:00, 20:00, 22:00, 24:00, 02:00, 04:00, 06:00 and 08:00 h; the nighttime samples were taken under dim red light. All blood samples were allowed to clot for 45 min, serum was removed after centrifugation, and stored at –20°C until assayed. Melatonin concentration was measured using RIA kit (DRG Inst. GmbH, Marburg; Cat. No. IH RE 29301, sensitivity 3.5 pg/ml, intra assay CV—8%, inter assay CV—14.8%). Statistical analysis of the data was performed using ANOVA and LSD (least significant difference) method according to Statgraphic plus V4 computer program.

The study was approved by the Regional Committee for Studies with Human Subjects (IEC). The experimental protocol was explained to each patient, and informed consent was obtained.

Results

There were no significant differences in circadian melatonin profiles (Fig. 1A) as well as in the area under curve (Fig. 1B) among the three main groups studied. Taking into consideration the type of tumor of the genital tract significantly lower melatonin secretion has been found in patients with endometrial cancer in comparison with tumor-free control groups (Fig. 2), whereas no significant differences in melatonin secretion have been observed between tumor-free control groups and patients with invasive ovarian cancer and squamous cervical cancer (Fig. 2). However, significant differences have been observed between endometrial cancer and invasive ovarian cancer (Fig. 2).

Discussion

Although alterations in melatonin concentrations have been reported in many studies, the results of these studies are contradictory [1–6]. Differences observed by various authors may depend on limited sampling approaches (one time point, during the daytime or two time points, at daytime and at night), various histological types of tumor, different

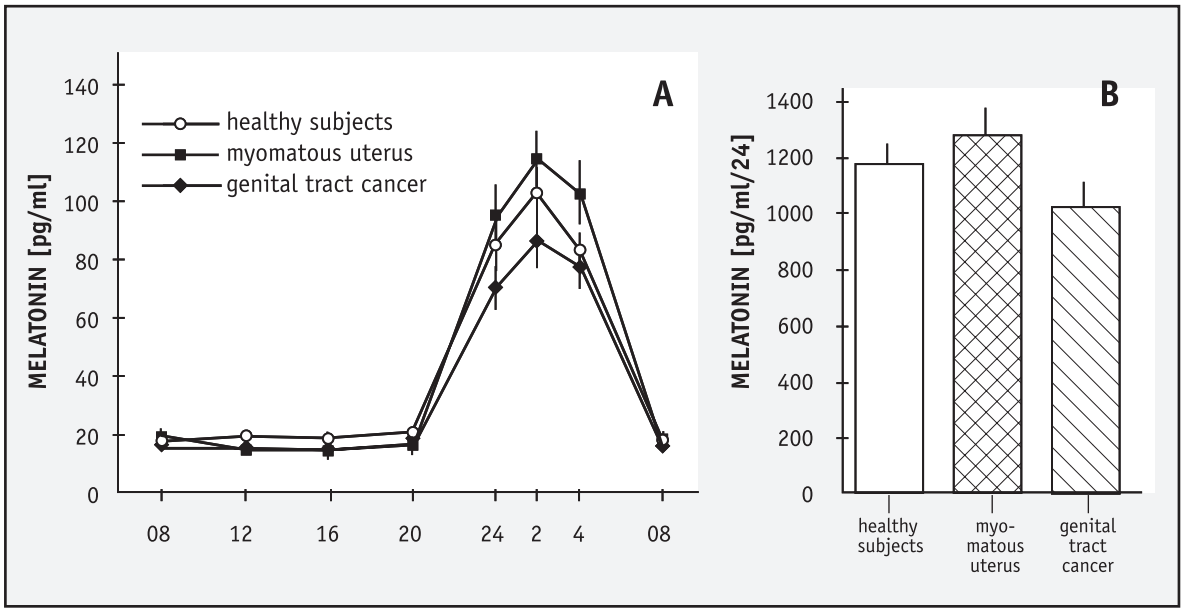

Fig. 1. Circadian melatonin profiles (**A**) and area under curve (**B**) in healthy volunteers, patients with myomatous uterus and patients suffering from genital tract tumors. No statistically significant differences.

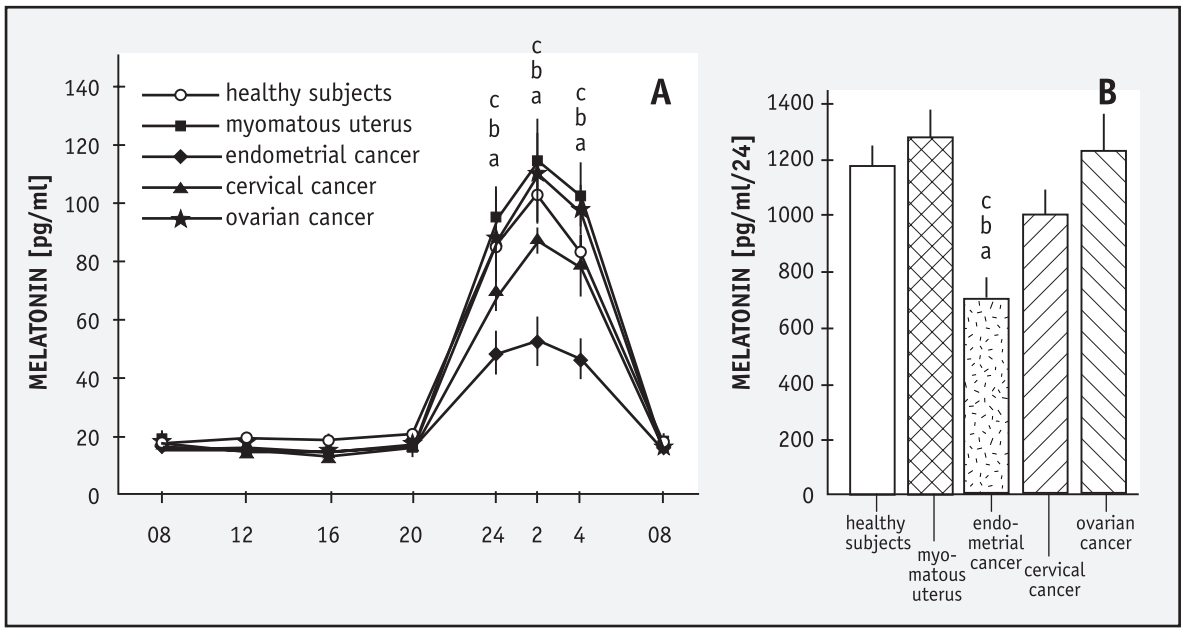

Fig. 2. Circadian melatonin profiles (**A**) and area under curve (**B**) in tumor-free subjects (healthy volunteers and patients with myomatous uterus) and patients suffering from various types of genital tract tumors (endometrial cancer, squamous cervical cancer and invasive ovarian cancer). Statistical significance: a—healthy subjects vs. endometrial cancer, $p<0.05$; b—myomatous uterus vs. endometrial cancer, $p<0.05$; c—endometrial cancer vs. invasive ovarian cancer, $p<0.05$.

stages of the neoplastic disease or not tightly controlled age-matching. Studies on circadian melatonin profiles in human neoplastic disease are relatively rare. Depressed melatonin plasma or urinary concentrations has been demonstrated in primary breast cancer [7–9]. However, Skene et al. [26] found that women with breast cancer (mean age 60.3 years) had significantly lower 24h urinary concentrations of 6-sulfatoxymelatonin than women with benign tumors (mean age 54.4 years) but when compared with a large group of 160 normal age-matched women (mean age 51.5 years), urinary 6-sulfatoxymelatonin levels in women with malignant tumors were not outside the normal range. It should be noted, however, that stage dependency in melatonin concentrations has been found when the peak declined with tumor size [8]. On the other hand, in recurrent breast cancer, melatonin concen-

trations were similar or even higher in comparison to healthy subjects [8, 9, 27].

Lower nocturnal serum melatonin concentrations and urinary 6-sulfatoxymelatonin excretion have been observed in patients suffering from prostate cancer in comparison to patients with benign prostate hyperplasia [10, 11].

Khoory and Stemme [12] who studied circadian plasma melatonin concentrations reported depression in melatonin nocturnal rise in colorectal carcinoma. Vician et al. [28] have found significant increase in melatonin concentration at 14.00h and 02.00h (the only time-points studied) after surgical treatment of colorectal carcinoma in comparison with values before surgery. However, the authors did not find differences in melatonin levels between patients with colon cancer and patients awaiting surgery for a chronic appendicitis, inguinal hernia and cholelithiasis, but it must be stressed that there were large age difference between both groups (67.7 and 27.1 years, respectively), and therefore such comparison is invalid.

No age differences between studied groups were observed in the present study, and therefore the subjects were tightly age-matched.

In a previous study we have found depressed nighttime serum melatonin concentrations in patients suffering from adenocarcinoma of the uterine corpus [13]. This observation has been confirmed in this tumor type in the present study, because depressed melatonin concentration has been found only in endometrial cancer (adenocarcinoma of the uterine corpus). It is worthy to note that Grin and Grunberger [29] have found significant correlation between daytime melatonin plasma concentrations and the presence of endometrial cancer (mean plasma value in cancer positive group—6.1 pg/ml, in cancer-negative group—33.2 pg/ml).

Interestingly, similar to breast cancer and prostate cancer, endometrial cancer is strongly gonadal hormone-dependent [30–34], whereas other two examined tumor types, i.e. squamous cervical cancer and invasive ovarian cancer, do not seem to be sensitive to estrogens and might be associated with genetic mutations rather than with hormonal factors, even if current literature does not allow firm conclusions to be drawn [30, 35–37]. Therefore, its seems probable that melatonin concentrations in human malignancy may, at least partly, depend on hormone dependency of the particular type of tumor.

Acknowledgments

This study was supported by a grant from the Medical University of Lodz, No. 502-11-415. The authors are grateful to Mr. Jacek Swietoslawski, M. Sc. for his help in the present work.

REFERENCES

1 Blask DE. The pineal gland: an oncostatic gland. In: Reiter RJ, editor. Pineal gland. New York: Raven Press; 1984. p. 253–84.
2 Blask DE. Melatonin in oncology. In: Yu HS, Reiter RJ, editors. Melatonin. Biosynthesis, physiological effects, and clinical applications. Boca Raton: CRC Press; 1993. p. 447–75.
3 Karasek (1994) Malignant tumors and the pineal gland. In: Gupta D, Wollmann HA, Fedor-Freybergh P, editors. Pathophysiology of immune-neuroendocrine communication circuit. Heidelberg: Mattes; 1994. p. 225–44.
4 Karasek M. Relationship between the pineal gland and experimentally induced malignant tumors. Front Horm Res 1997; **23**:99–106.
5 Karasek M, Pawlikowski M. Pineal gland, melatonin and cancer. Neuroendocrinol Lett 1999; **20**:139–144.
6 Karasek M. Melatonin in human neoplastic disease. Int J Thymol 1996; **4**(**suppl. 1**):75–79.
7 Bartsch C, Bartsch H, Laumas KR, Wetterberg L. Urinary melatonin levels in human breast cancer patients. J Neural Transm 1981; **52**:281–94.
8 Bartsch C, Bartsch H, Fuchs U, Lippert TH, Bellmann O, Gupta D. Stage-dependent depression of melatonin in patients with primary breast cancer. Cancer 1989; **64**:426–33.
9 Bartsch C, Bartsch H, Bellman O, Lippert TH. Depression of serum melatonin in patients with primary breast cancer is not due to an increased peripheral metabolism. Cancer 1991; **67**:1681–4.
10 Bartsch C, Bartsch H, Flüchter SH, Harzmann R, Attanasio A, Bichler KH, et al. Circadian rhythms of serum melatonin, prolactin and growth hormone in patients with benign and malignant tumours of the prostate and in non-tumor controls. Neuroendocrinol Lett 1983; **5**:377–86.
11 Bartsch C, Bartsch H, Schmidt A, Ilg S, Bichler KH, Flüchter SH. Melatonin and 6-sulfatoxymelatonin circadian rhythms in serum and urine of primary prostate cancer patients: evidence for reduced pineal activity and relevance of urinary determinations. Clin Chim Acta 1992; **209**:153–76.
12 Khoory R, Stemme D. Plasma melatonin levels in patients suffering from colorectal carcinoma. J Pineal Res 1988; **5**:251–8.
13 Karasek M, Dec W, Kowalski AJ, Bartsch H, Bartsch C. Serum melatonin circadian profile in women with adenocarcinoma of uterine corpus. Int J Thymol 1996; **4**(**suppl. 1**):80–83.
14 Blask DE, Hill SM. Studies on MCF-7 human breast cancer cells in culture. J Neural Transm 1986; **Suppl. 21**:433–49.
15 Hill SM, Blask DE. Effects of the pineal hormone melatonin on the proliferation and morphological characteristics of human breast cancer cells (MCF-7) in culture. Cancer Res 1988; **48**:6121–6.

16 Persengiev SP, Kyurkchiev S. Selective effects of melatonin on the proliferation of lymphoid cells. Int J Biochem 1993; **25**:441–4.
17 Sze SF, Ng TB, Liu WK. Antiproliferative effect of pineal indoles on cultured tumor cell lines. J Pineal Res 1993; **14**:27–33.
18 Ying SW, Niles LP, Crocker C. Human malignant melanoma cells express high-affinity receptors for melatonin: antiproliferative effects of melatonin and 6-chloromelatonin. Eur J Pharmacol 1993; **246**:89–96.
19 Cos S, Verduga R, Fernandez-Viadero C, Megias M, Crespo D. Effects of melatonin on the proliferation and differentiation of human neuroblastoma cells in culture. Neurosci Lett 1996; **216**:113–6.
20 Hu DN, Roberts JE. Melatonin inhibits growth of cultured human uveal melanoma cells. Melanoma Res 1997; **7**:27–31.
21 Lupowitz Z, Zisapel N. Hormonal interactions in human prostate tumor LNCaP cells. J Steroid Biochem Mol Biol 1999; **68**:83–8.
22 Leone AM, Silman RE, Hill BT, Whelan RDH, Shellard SA. Growth inhibitory effects of melatonin and its metabolites against ovarian tumour cell lines in vitro. In: Gupta D, Attanasio A, Reiter RJ, editors. The pineal gland and cancer. London: Brain Research Promotion; 1988. p. 273–81.
23 Shellard SA, Whelan RDH, Hill BT. Growth inhibitory and cytotoxic effects of melatonin and its metabolites on human tumour cell lines *in vitro*. Br J Cancer 1989; **60**:288–90.
24 Petranka J, Baldwin W, Biedermann J, Jayadev S, Barrett JC, Murphy E. The oncostatic action of melatonin in an ovarian carcinoma cell line. J Pineal Res 1999; **26**:129–36.
25 Chen LD, Leal BZ, Reiter RJ, Abe M, Sewerynek E, Melchiori D, et al. Melatonin's inhibitory effect on growth of ME-180 human cervical cancer cells is not related to intracellular glutathione concentrations. Cancer Lett 1995; **91**:153–9.
26 Skene D, Bojkowski CJ, Currie JE, Wright J, Boulter PS, Arendt J. 6-Sulfatoxymelatonin production in breast cancer patients. J Pineal Res 1990; **8**:269–76.
27 Karasek M, Kuzdak K, Cywinski J, Zylinska K, Smialowska A, Pluzanska A. Effects of melatonin administration in advanced breast cancer patients – preliminary report. Neuroendocrinol Lett 1998; **19**:15–9.
28 Vician M, Zeman M, Herichova I, Jurani M, Blazicek P, Matis P. Melatonin content in plasma and large intestine of patients with colorectal carcinoma before and after surgery. J Pineal Res 1999; **27**:164–9.
29 Grin W, Grunberger W. A significant correlation between melatonin deficiency and endometrial cancer. Gynecol Obstet Invest 1998; **45**:62–5.
30 Hoffman PG, Siiteri PK. Sex steroid receptors in gynecologic cancer. Obstetr Gynecol 1980; **55**:648–52.
31 Dietrich W. New aspect of steroid hormone dependent tumor growth. Arch Geschwulstforsch 1990; **60**:149–60.
32 Miller WR, Langdon SP. Steroid hormones and cancer: (III) Observations from human subjects. Eur J Surg Oncol 1997; **23**:163–83.
33 Jenster G. The role of the androgen receptor in the development and progression of prostate cancer. Semin Oncol 1999; **26**:407–21.
34 Fujimoto J, Horose R, Sakaguchi H, Tamaya T. Estrogen dependency in uterine endometrial cancers. Oncology 1998; **55**(suppl. 1):53–9.
35 Gadducci A, Fanucchi A, Cosio S, Genazzani AR. Hormone replacement therapy and gynecological cancer. Anticancer Res 1997; **17**:3793–8
36 Shushan A, Paltiel O, Schenkler JG. Induction of ovulation and borderline ovarian cancer—the hormonal connections? Eur J Obstet Gynecol Reprod Biol 1999; **85**:71–4.
37 Ciocca DR, Puy LA, Fasoli LC. Study of estrogen receptor, progesterone receptor, and the estrogen-regulated Mr 24,000 protein in patients with carcinomas of the endometrium and cervix. Cancer Res 1989; **49**:4298–304.