Obesity Facts

Review Article

Obes Facts 2023;16:131–140
DOI: 10.1159/000527691

Received: February 1, 2022
Accepted: October 10, 2022
Published online: November 8, 2022

The EASO New Investigator Award in Clinical Research 2021: Role of Chronotype in Obesity

Giovanna Muscogiuri[a, b, c]

[a]Dipartimento di Medicina Clinica e Chirurgia, Unità di Endocrinologia, Diabetologia ed Andrologia, Università Federico II di Napoli, Naples, Italy; [b]Centro Italiano per La Cura e Il Benessere Del Paziente con Obesità (C.I.B.O), Department of Clinical Medicine and Surgery, Endocrinology Unit, University Medical School of Naples, Naples, Italy; [c]Cattedra Unesco "Educazione Alla Salute e Allo Sviluppo Sostenibile", Università Federico II di Napoli, Naples, Italy

Keywords
Chronotype · Obesity · Cardiometabolic diseases · Cancer · Insulin resistance · Type 2 diabetes

Abstract
Background: Chronotype is the expression of the timing of circadian rhythmicity of a subject, and three categories of chronotype have been identified: morning, evening, and intermediate chronotype. Subjects with morning chronotype prefer to carry out most of their daily activities in the morning, while subjects with evening chronotype perform most of their daily activities in the second half of the day. Intermediate chronotype is in an intermediate position between the above reported categories. Recently, evening chronotype has been associated with an increased risk of developing chronic diseases. Thus, the aim of this manuscript was to review the current evidence on the role of chronotype categories on the risk of developing obesity and the most common obesity-related comorbidities (cardiometabolic and neoplastic complications). ***Summary:*** Subjects with evening chronotype have been reported to be at high risk of developing obesity, and this was mostly due to the tendency of these subjects to follow unhealthy lifestyle mostly characterized by sedentary behavior and high intake of unhealthy food. In addition, sleep disturbances are a common finding in subjects with evening chronotype that in turn could further contribute to the risk of obesity. The impairment of insulin sensitivity, melatonin, adiponectin, and clock genes function along with increase of leptin secretion detected in subjects with evening chronotype could also represent a favorable milieu for the onset of obesity-related cancer. The current evidence is limited to breast, prostate, and endometrial cancer. ***Key Messages:*** The chronotype categories could be easy assessed in subjects with obesity and at the same time provide an important information on an additional risk factor predisposing to the onset of obesity-related comorbidities. Since chronotype could be potentially modified through a behavioral-driven approach thus potentiating the efficacy of anti-obesity treatment, the assessment of chronotype categories should be included in the management of obesity.

Introduction

Chronotype is the attitude of the subject to carry out most of the daily activities in a certain time of the day [1]. In particular, morning chronotype is the subject that prefers to carry out his/her activity in the morning, while

Karger@karger.com
www.karger.com/ofa

Correspondence to:
Giovanna Muscogiuri, giovanna.muscogiuri@gmail.com

evening chronotype prefers to carry out his/her activity in the evening. Intermediate chronotype is in an intermediate position between morning and evening chronotypes [1]. It has been demonstrated that chronotype categories could have an impact on the risk of developing obesity and obesity-related comorbidities. Subjects with evening chronotype are more prone to follow unhealthy lifestyle, and this could result in an increased risk of developing obesity [2–4]. We previously demonstrated that subjects with evening chronotype had lower adherence to the Mediterranean diet (MD) and that the cluster of the MD and not a single food was associated with chronotype categories [2]. Subjects with evening chronotype are also at higher risk of sleep disturbances that in turn are well-known risk factors for obesity [5–8]. In particular, evening chronotype has been associated with an increased risk of developing and worsening type 2 diabetes (T2D) [9]. In a study carried out by Reutrakul et al. [9], 194 subjects with T2D were enrolled and underwent to the assessment of chronotype and sleep disturbances. The main finding of this study was that evening chronotype was associated with poorer glycemic control independently of sleep disturbances [9]. In addition, we found that chronotype has been reported to play an important role in the obesity-related cardiometabolic risk [10]. Indeed, evening chronotype has been reported to be associated with hypertension and higher levels of serum total cholesterol, and low-density lipoprotein cholesterol than morning chronotypes in a larger cross-sectional analysis of the national FINRISK 2007 study including 6,528 individuals of the Finnish population [10]. Finally, it is well known that obesity could predispose to some type of cancers that recognize in metabolic derangements a key role in their pathogenesis. Indeed, in the California Teachers Study (CTS), evening chronotype has been reported to be an independent risk factor for breast cancer in 36,967 postmenopausal women [11]. Thus, the aim of this manuscript was to review the current evidence on the role of chronotype in obesity and obesity-related comorbidities and to provide physiopathological insights on these associations.

Chronotype and Obesity

Several evidence reported evening chronotype to be a risk factor for obesity [3, 4, 12]. Sun et al. [3] carried out a study in 1,197 middle-aged men and women (mean age 48.2 ± 5.3 years) who participated in the Bogalusa Heart Study 2013–2016. Chronotype categories were assessed by Morningness-Eveningness Questionnaire (MEQ), and obesity was defined as a body mass index (BMI) ≥30 kg/m^2. Eleven percent of participants were found to belong to evening chronotype that in turn was associated with obesity after multivariable adjustment, including shift work, physical activity, and sleep duration [3]. The link between obesity and evening chronotype has been also found in a cross-sectional study carried out in 110 drug-naive children and adolescents aged 7–17 years with attention deficit hyperactivity disorder (ADHD) diagnosed using The Kiddie Schedule for Affective Disorders and Schizophrenia-Present and Lifetime Version (K-SADS-PL) [4]. The severity of ADHD symptoms and chronotype categories were assessed by the Conners' Parents Rating Scale-Revised Short Version (CPRS-RS) and Children's Chronotype Questionnaire (CCQ), respectively. BMI was calculated and classified according to national age- and gender-specific reference values. The prevalence of morning chronotype (86.84%) was higher in children with normal BMI, while the prevalence of evening chronotype (61.90%) was higher in children with obesity. Independently from ADHD symptoms, evening chronotype was directly related to obesity, while morning chronotype was directly related to normal weight [4]. Also, in a cross-sectional study enrolling 245 pregnant women attending the public health service in Brazil was demonstrated that evening chronotype, assessed by the time of mid-sleep time on free days with a further correction for calculated sleep debt, was associated to a weight gain during the early gestational period [12]. The association between evening chronotype and obesity could be explained by several links. First, it has been reported that evening chronotype was associated with unhealthy lifestyle [2]. We investigated the association of chronotype categories with adherence to the MD in a population of middle-aged Italian adults [2]. In this cross-sectional study enrolling 172 middle-aged adults (71.5% females; 51.8 ± 15.7 years) during a campaign to prevent obesity called the OPERA (obesity, programs of nutrition, education, research and assessment of the best treatment) Prevention Project that was held in Naples on 11–13 October 2019 [13], chronotype categories were assessed by MEQ. The prevalence of morning, evening, and intermediate chronotypes was 58.1%, 12.8%, and 28.1%, respectively. Subjects with evening chronotype followed unhealthy lifestyle, performing less regular activity, and being more frequently smokers. In addition, they reported the lowest adherence to the MD compared to the other chronotype categories. Consequently, this resulted in the highest BMI value in this category [2]. Data from the UK Biobank, a prospective

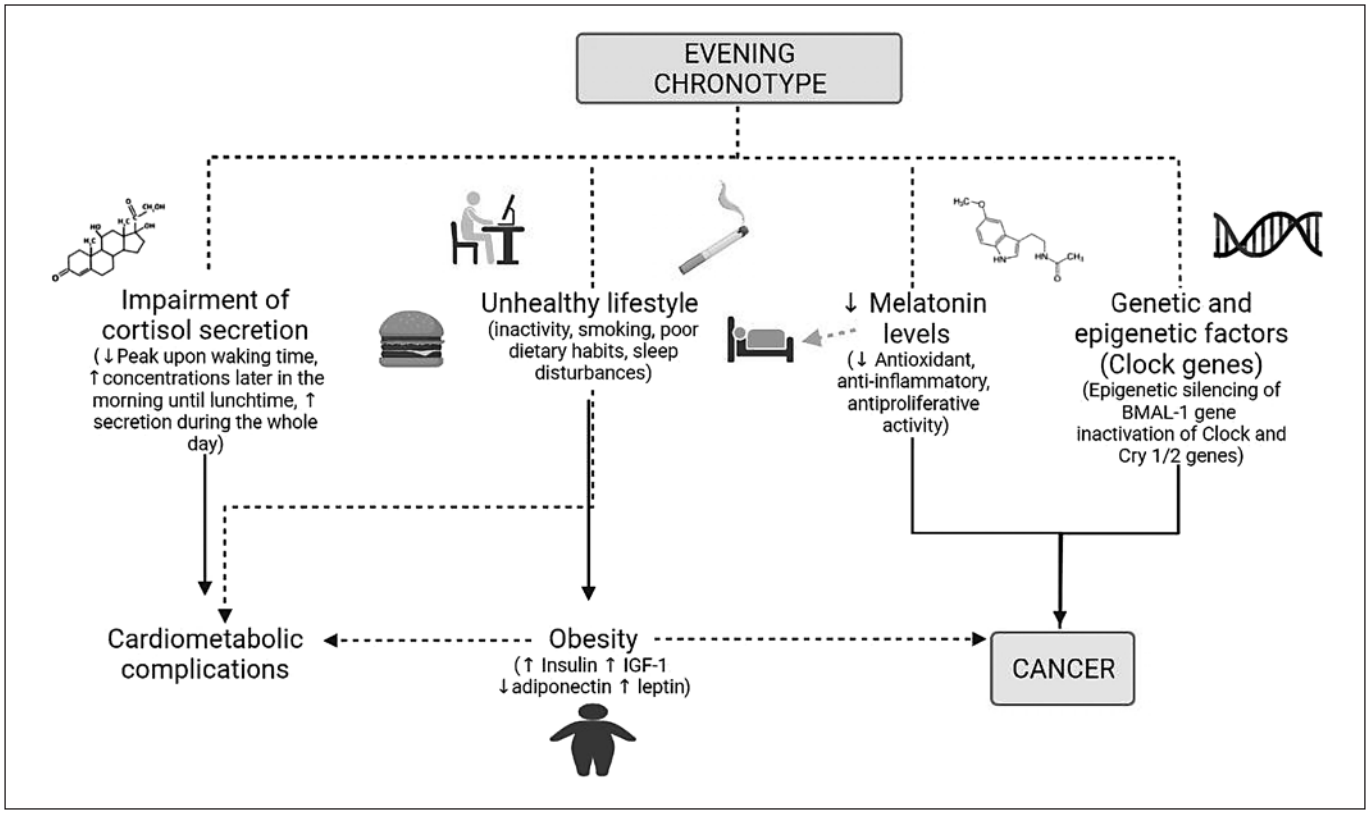

Fig. 1. Mechanisms linking evening chronotype to obesity and obesity-related comorbidities. Subjects with evening chronotype perform most of their daily activities in the second half of the day. Evening chronotype has been associated with an increased risk of developing obesity and the most common obesity-related comorbidities (cardiometabolic and neoplastic complications). Indeed, subjects with evening chronotype have been reported to be at high risk of developing obesity due to their tendency to follow unhealthy lifestyle mostly characterized by sedentary and low intake of healthy food. In addition, sleep disturbances are a common finding in subjects with evening chronotype that in turn could further contribute to the risk of obesity and cardiometabolic complications. Evening chronotype is also characterized by an impairment of cortisol secretion as compared to morning chronotype. In particular, evening chronotype presents a lower cortisol peak upon waking time, while higher cortisol concentrations later in the morning until lunchtime, and greater cortisol secretion during the whole day. Hyperactivity of the hypothalamic-pituitary-adrenal axis leading to hypercortisolism, results in a further visceral adipogenesis, thus worsening insulin resistance. The impairment of insulin resistance, melatonin, adiponectin, and leptin secretion and clock genes function detected in subjects with evening chronotype could also represent a favorable milieu for the onset of obesity-related cancer.

cohort study that began in 2005 using patient registers from the UK National Health Service (NHS), adults aged 40–69 years who live within a 10-mile radius of one of the UK Biobank's 35 assessment center, reported that subjects with morning chronotype as assessed by MEQ were more prone to consume a mean of 0.25 more servings of vegetables as assessed by the 24 h recalls than subjects with evening chronotype [14]. A lower intake of whole grains, rye, potatoes, vegetables, and roots and a higher intake of wine and chocolate has also been reported in subjects with evening chronotype, assessed by a shortened version of MEQ in a sample of the 4,493 subjects from the National FINRISK 2007 Study [15]. In this study, dietary data were collected using a validated food frequency questionnaire [15]. Similarly, a lowest adherence to the Baltic Sea dietary pattern and a highest tendency to be smokers and physically inactive than other chronotypes have been reported in the study by Maukonen et al. [16] carried out in 4,421 subjects aged 25–74 years of the National FINRISK 2007 Study. Baltic Sea diet score (BSDS), including nine dietary components, was used as a measure of adherence to a healthy Nordic diet, while chronotype was assessed using a shortened version of MEQ [16]. Evening chronotype has also been reported to be associated with sleep disturbances [17] that in turn are frequently associated with obesity [5, 7, 8, 18].

Indeed, sleep deprivation (4 h per night over 2 days) has been reported to result in a higher appetite score and hunger assessed using a visual analog scale than regular sleep duration (10 h per night over 2 days), accompanied by a tendency to prefer high carbohydrate and high-fat food intake [19]. Subjects with sleep deprivation experienced an increase in plasma ghrelin and decrease in plasma leptin secretion [20]. This finding was confirmed in the study by Chaput et al. reporting reduced levels of leptin and increased levels of ghrelin in subjects with short sleep duration suggesting that short sleep may affect appetite modifying appetite-regulating hormones level [21]. Sleep deprivation for 6 consecutive days was associated with a decrease of leptin levels that was kept for 24 h [22]. A leptin resistance condition has been reported in subjects with obstructive sleep apnea in which the weight-reducing effects of leptin are damaged, therefore inducing a vicious cycle of weight gain and worsening obstructive sleep apnea [21]. Although no final conclusions were drawn from studies investigating the association of sleep duration with dietary consumption [23–25], the decreased sleep time may result in an increased chance to eat mostly if most of the wake time is spent in an environment with readily available food [26]. In addition, a decrease in physical activity is the obvious consequence of the tiredness resulting from sleep deprivation [27]. Indeed, short sleep duration has been reported to be associated with increased sedentary lifestyle (e.g., viewing television and reduced sport time) in children [25] as well as in adults [24, 25, 27, 28] (shown in Fig. 1). In conclusion, evening chronotype predisposes to obesity acting through different mechanisms that include unhealthy lifestyle, i.e., reduced physical activity along with unhealthy diet, and sleep disturbances that are also known risk factors for obesity.

Chronotype and Cardiometabolic Complications

The circadian system is known to be important in the regulation of glucose metabolism [29]. A cross-sectional study carried out in 1,014 non-shift working adults with prediabetes reported that later mid-sleep time on free day adjusted for sleep debt, an indicator of chronotype but not social jetlag was significantly associated with higher glycated hemoglobin-A1c (HbA1c) levels [30]. In addition, after adjusting for age, sex, alcohol use, BMI, social jetlag, sleep duration, sleep quality, and sleep apnea risk, later mid-sleep time on free day adjusted for sleep debt was significantly associated with higher HbA1c level, thus leading to conclude that later chronotype was associated with higher HbA1c levels in patients with prediabetes, independent of social jetlag and other sleep disturbances [30]. Similar results were found in 172 middle-aged adults (71.5% females: 51.8 ± 15.7 years) [31]. Fifty-eight percent of these subjects were classified as morning, 12.8% as evening, and 28.1% as intermediate. Beyond an unhealthier lifestyle than other chronotypes, subjects with evening chronotype had significantly higher risk to have T2D and cardiovascular diseases compared to morning chronotype after adjustment for gender, BMI, sleep quality, and adherence to the MD [31]. These findings were also confirmed in a cross-sectional study carried out in postmenopausal women [32]. In this cross-sectional study, we enrolled 49 premenopausal and 74 postmenopausal women with obesity. Anthropometric parameters, lifestyle habits, adherence to the MD, sleep quality, chronotype, and the presence of T2D and cardiovascular diseases were studied. No significant differences were detected in terms of lifestyle and adherence to the MD between pre- and postmenopausal women. In this population, 53.6% of women were found to have morning chronotype, 16.3% evening chronotype, while 30.1% intermediate chronotype. Although premenopausal women with obesity had a significantly higher prevalence of intermediate chronotype than postmenopausal women, in both groups, evening chronotype was associated with an increased risk of having T2D [32]. Subjects with T2D and evening chronotype have been reported to have a worse metabolic control than other chronotype categories [9]. This cross-sectional study was carried out in 192 diabetic subjects in which chronotype categories were assessed using validated construct derived from mid-sleep time on weekends, while 1-day food recall was used to compute the temporal distribution of caloric intake. Interestingly, each hour delay in mid-sleep time on weekends was associated with a modestly but significantly higher HbA1c of 2.5% of its original value after adjusting for age, sex, race, BMI, depressive symptoms, diabetes complications, insulin use, and sleep parameters. Latter subjects with evening chronotype reported to consume a greater percentage of their daily caloric intake at dinner compared with other chronotype categories, although the association with chronotype was only slightly decreased after adjustment for daily calorie distribution at dinner [9]. The link between chronotype categories and glucose metabolism includes several causes. First, evening chronotype is characterized by an impairment of cortisol secretion as compared to morning chronotype. In particular, evening chronotype presents a lower cortisol peak upon waking

Table 1. Epidemiological studies evaluating the relationship between chronotype categories and neoplastic diseases

References	Study design	Type of endocrine cancers	Results
Hurley et al., 2019 [11]	Retrospective case-control study	Breast cancer	Eveningness is associated with a slightly increased risk of breast cancer (OR 1.20, 95% CI: 1.05–1.37)
Hahm et al., 2014 [44]	Retrospective cross-sectional study	Breast cancer	Morningness is associated with longer DFI in patients with bedtime misalignment (HR 0.539, 95% CI: 0.320–0.906)
Lee et al., 2017 [45]	Prospective observational study	Breast cancer	Eveningness is associated with higher rates of CINV in patients treated with neoadjuvant chemotherapy for breast cancer (OR 3.53, 95% CI: 1.27–9.79, $p = 0.015$)
Son et al., 2020 [47]	Prospective observational study	Breast cancer	Morningness is associated with lower rates of CIHF in patients treated with adjuvant chemotherapy for breast cancer (OR 0.37, 95% CI: 0.13–0.96, $p = 0.045$)
Dickerman, et al. 2016 [43]	Prospective observational study	Prostate cancer	Eveningness is associated with a significantly increased risk of prostate cancer (HR 1.3; 95% CI: 1.1, 1.6)
Lozano-Lorca et al., 2020 [46]	Population-based case-control study	Prostate cancer	Eveningness is associated with a higher risk of prostate cancer in shift workers (OR 3.14, 95% CI: 0.91–10.76)
Sun et al., 2021 [48]	Two-sample mendelian analysis conducted on 268 SNPs associated with morning chronotype	Prostate cancer	Genetically predicted morningness is associated with a lower risk of prostate cancer (OR 0.71, 95% CI: 0.54–0.94, $p = 0.019$)
Von Behren et al., 2021 [49]	Retrospective case-control study	Endometrial cancer	Eveningness is associated with a higher risk of endometrial cancer (OR 1.44, 95% CI: 1.09–1.91)

OR, odds ratio; CI, confidence interval; DFI, disease-free interval; CIHF, chemotherapy-induced hot flashes; CINV, chemotherapy-induced nausea and vomiting; SNP, single nucleotide polymorphisms.

time [33, 34] and higher cortisol concentrations later in the morning until lunchtime [33]. Hyperactivity of the hypothalamic-pituitary-adrenal axis leading to hypercortisolism, as detected in obesity, results in a further visceral adipogenesis thus worsening insulin resistance [35, 36]. Therefore, the impairment of cortisol secretion might explain, at least in part, the worse metabolic control in subjects with T2D and evening chronotype. Second, subjects with evening chronotype are more prone to eat unhealthy diet and to perform less regular activities; both these characteristics are well-known enemies of metabolic control [2]. Third, subjects with evening chronotype mimicked the behavior detected in Clock mutant mice that were shown to shift their feeding and activity into their normally inactive phase, thus developing obesity and obesity-related metabolic complications [37]. This suggests that evening chronotype could be also a spy of some genetic alteration that at the same time predisposes also to metabolic derangement and this was the case of certain genotypes of clock and brain and muscle Arnt-like protein 1 (BMAL-1) [38–40]. Finally, subjects with evening chronotype are more prone to develop sleep disturbances [41] that through several mechanisms contribute to deteriorate glucose metabolism [42]. Evening chronotype has been also associated with an increased risk of developing cardiovascular diseases [31]. This was due not only to the increased risk of developing T2D but also to the increased risk of developing hypertension [10]. The National FINRISK Study 2007 carried out in 6,258 subjects, being a representative sample of the population aged 25 to 74 years living in five areas of Finland, showed that subjects with evening chronotype had a 1.3-fold odds ratio for arterial hypertension and a faster resting heart rate and a lower systolic blood pressure than subjects with morning chronotype [10] (shown in Fig. 1). Based on these evidence evening chronotype could be considered as risk factor for cardiometabolic complications in obesity, mostly having an impact on glucose metabolism and blood pressure.

Chronotype and Obesity-Related Cancers

Although there are currently scarce data regarding the association of chronotype categories and cancers, chronotype could be considered a spy of circadian rhythm,

and thus, it could be used as a tool to detect circadian misalignment that in turn has been associated with the risk of developing obesity-related cancers [11, 43–49]. Indeed, the most studied human model of circadian misalignment is shiftwork that has been defined by the International Agency for Research on Cancer [50, 50] as a potential carcinogenic factor [50]. The individual preference of daily cycle which is represented by chronotype is set up by a combination of genetic and epigenetic factors that have influence on physical and mental health [51]. Specifically, in mammals, circadian rhythms are regulated by a set of circadian genes, also known as clock genes. First of all, it has been demonstrated that clock-related genes that regulate the function of the circadian clock are also involved in oncostatic activity. In fact, epigenetic silencing of BMAL-1 gene has been reported to increase the risk of developing hematological cancers, while the inactivation of Clock and Cry 1/2 genes result in an increased risk of solid tumors such as prostate, hepatocellular, ovarian cancer, and pleural mesothelioma [52]. Furthermore, in subjects with evening chronotype, lower levels of melatonin have been detected compared to subjects with morning chronotype [53], and melatonin has been shown to have antioxidant (via stimulation of antioxidant enzymes such as glutathione reductase), anti-inflammatory (via inhibition of NF-KB pathway), and antiproliferative properties (via inhibition of PI3K/Akt, IGF1-R, and HIF-1 pathways) [54]. Thus, a reduction in melatonin levels that frequently occurs in evening chronotype could promote cell proliferation and pro-inflammatory activity, and consequently an increased risk of neoplastic transformation [55] (shown in Fig. 1). Here, we reported the current evidence on obesity-related cancer for which it has been also hypothesized a role for chronotype categories as neoplastic risk factor (Table 1).

Breast Cancer

Breast cancer is the most common cancer in women [56], and it has been reported to be more prevalent in women with obesity [57]. This is because adipose tissue inflammation represents a favorable milieu for the development of cancer. Indeed, high levels of leptin often detected in subjects with obesity as compensatory mechanism to leptin resistance could play a role in promoting cancer survival, proliferation, and metastasis through the binding of leptin receptors expressed in human breast cancer [58]. Furthermore, resistin primarily secreted by macrophages not only mediates insulin resistance thus inducing compensatory hyperinsulinemia, a well-known risk factor for cancer, but also encourages human breast cancer cell growth and metastasis-activating Stat3 and the ERM family of proteins [59–62]. Finally, adiponectin that is known to suppress the survival and proliferation of human breast cancer cells [63] and to inhibit carcinogenesis [64, 65] has been found to be significantly lower in postmenopausal women with breast cancer [66]. Additional risk factors to obesity, such as prolonged exposure to estrogen due to early menarche and delayed menopause smoking and alcohol have been identified [67]. Recently, chronotype categories have been also hypothesized to play a role in the context of breast cancer [11, 44, 45, 47]. Indeed, a case-control study nested within the CTS cohort enrolled 39,686 postmenopausal women [11]. Chronotype was assessed by responses to an abbreviated version of MEQ. Women with evening chronotype had an increased risk of breast cancer with elevated ORs compared to other chronotype categories thus suggesting that evening chronotype may be an independent risk factor for breast cancer in women who are not known to have engaged in any substantial night shift work [11]. A retrospective study was carried out in 85 women with metastatic breast cancer in which chronotype and alignment of actual bedtime with preferred chronotype were examined using the MEQ and sleep-wake log [44]. The median disease-free interval (DFI) was 81.9 months for women with aligned bedtimes ("going to bed at preferred bedtime"), while it was 46.9 months for women with misaligned bedtimes ("going to bed later or earlier than the preferred bedtime"). After adjustment for several factors influencing DFI such as chronotype, estrogen receptor status at initial diagnosis and level of natural-killer cell count, misaligned bedtimes, often detected in subjects with evening chronotype, was associated with shorter DFI compared to aligned bedtimes [44]. Although chronotype categories seem to have an impact on incidence and course of breast cancer, it seems to also play a role in response to treatment [45]. Indeed, a prospective observational study carried out in women with breast cancer who planned to be treated with neoadjuvant chemotherapy before surgery reported that overall chemotherapy-induced nausea and vomiting were significantly associated with evening chronotype in addition to a history of nausea/vomiting [45]. Furthermore, the impact of chronotype categories has been also investigated in a total of 119 premenopausal women with nonmetastatic breast cancer awaiting adjuvant chemotherapy after surgery without hot flashes were included [47]. The presence of chemotherapy-induced hot flashes was defined as having moderate to severe hot flashes, as measured by the subscale of hot flashes in the Menopause Rating Scale, at 4 weeks after the completion of chemothera-

py. Chronotype assessment was done using the Composite Scale of Morningness before adjuvant chemotherapy. The main finding of this study was that morning chronotype was inversely associated with chemotherapy-induced hot flashes, also after adjustment for age, BMI, sleep quality, and radiation therapy [47]. Based on this evidence, the assessment of chronotype categories should be taken into account in the prediction and management of breast cancer.

Prostate Cancer

Prostate cancer has been reported to be the most common cancer in males [68] and recognizes obesity to play a role in its pathogenesis [69]. This is due to the effect of compensatory hyperinsulinemia to insulin resistance often detected in obesity and to the alteration of sex hormone blood concentrations (decreased serum testosterone and peripheral aromatization of androgen) [70]. In addition, visceral obesity and hyperinsulinemia are associated with hypersecretion of IGF-1, a growth factor that is involved in mitogenesis, proangiogenesis, and inhibition of apoptosis encouraging the cancer progression [70]. Hyperinsulinemia is also associated with low plasmatic concentrations of sex hormones, which may ultimately contribute to the development of poorly differentiated prostate cancer [71]. This effect occurs through the inhibition of hepatic sex hormone-binding globulin synthesis thus resulting in an increase in the levels of nonbound testosterone and dihydrotestosterone that in turn blocks the luteinizing hormone secretion, thus inhibiting the testicular androgen synthesis [71]. As a consequence, men with obesity reported low levels of sex hormone-binding globulin, luteinizing hormone, and testosterone. The increase in leptin levels along with the decrease in adiponectin levels could be an additional mechanism that contributes to the development of prostate cancer in men with obesity [72, 73]. This is because adiponectin has been reported to have antitumor effects by inhibiting cancer cell growth and by inhibiting inflammation, while leptin has been reported to have a pro-tumor effect in human prostate cancer cell lines by increasing the expression of antiapoptotic proteins, inflammatory markers (tumor necrosis factor-alpha [TNFα] and interleukin 6 [IL6]), and angiogenic factors [72, 73]. Finally, the increased oxidative stress coming from hypoxia and ischemia due to obstruction of capillaries of hypertrophic adipocytes damages the cell DNA [74]. All the above reported mechanisms result in increased proliferation, decreased apoptosis, and, eventually, DNA mutations of prostate cancer cells.

There are still few scientific evidence supporting an association of chronotype and prostate cancer. A case-control study was carried out in 465 males with prostate cancer and 410 controls [46]. The aggressiveness of prostate cancer was determined according to the International Society of Urology Pathology classification. Night shift workers were more prone to develop prostate cancer, especially, rotating night shifts and this association was amplified in males with evening chronotype [46]. Data drawn from the Older Finnish Twin Cohort including 11,370 twins followed from 1981 to 2012 reported 602 incident cases of prostate cancer and 110 deaths from prostate cancer [43]. In this study, evening chronotype was associated with a significantly increased risk of prostate cancer than morning chronotypes [43]. Given the evidence provided by observational epidemiological studies, a study was carried out in order to investigate the potential causal relationship between chronotype and prostate cancer risk using a Mendelian randomization design [48]. A total of 268 single nucleotide polymorphisms associated with chronotype were selected from a meta-analysis of genome-wide association studies of 697,828 individuals finding that genetically predicted morningness (scaled to a sleep midpoint of 1 h earlier) had a reduced risk of prostate cancer, with an odds ratio of 0.71 (95% confidence interval: 0.54–0.94 by IVW), compared with the eveningness thus suggesting a causal protective effect of morning chronotype on the risk of prostate cancer [48].

Endometrial Cancer

Endometrial cancer has been reported to be one of the most prevalent in women with obesity [75]. Beyond being a risk factor for development of cancer, obesity seems also to play a role in the risk of recurrence and death from cancer [75]. The increased amount of adipose tissue as detected in women with obesity predispose to the increased aromatization of androstenedione to estrone that in turn drives to the development of type 1 endometrial cancer through activation of the estrogen receptor, ERα [76]. In addition, the imbalance between adiponectin and leptin that occurs in obesity is also thought to contribute to endometrial carcinogenesis.

There are few data regarding the link between chronotype and endometrial cancer. A study was carried out in women that were members of the CTS cohort, which was established in 1995 [49]. Chronotype was assessed through a subsequent questionnaire (Q5), administered in 2012–2013. The cancer cases were 437, identified through linkages to the California Cancer Registry, and were diag-

nosed between 1996 and 2014, while cancer-free controls were 26,753. The prevalence of morning chronotype was higher in the controls than in cancer cases (39% and 34%, respectively). Evening chronotype was associated with the risk of developing endometrial cancer, and this was more pronounced in women with obesity. However, because this study was based on a retrospective analysis in a cohort of mostly white female teachers in California, further studies on chronotype categories as a potential endometrial cancer risk factor should be carried out [49].

Conclusion

Evening chronotype could represent a risk factor for developing obesity and obesity-related complications such as cardiometabolic and neoplastic comorbidities. Since it has been reported that nutritional challenges are able to reprogram "the clock" and that chronotype could be also a consequence of (caused by) the entraining effect of food constituents or eating patterns on the peripheral clocks, evening chronotype might be susceptible of behavioral modifications, potentially switching to morning or intermediate chronotype after nutritional challenges. As well known, the most currently used nutritional approaches for metabolic diseases are represented by the MD and very-low calorie ketogenic diet. Although it has not been reported evidence on the effect of the MD on circadian rhythm, it could be hypothesized that the food cluster of the MD could play a role in this sense as suggested by the property of the MD to improve sleep quality in subjects with obesity.

Similarly, in a study carried out in fed mice with ketogenic diet or normal chow for 2 weeks, it has been observed that ketogenic diet induced a phase-advance in peripheral clocks and behavioral activity, despite a maintained light-dark cycle and feeding ad libitum. The phase-advance in circadian rhythm results in bedtime and wake-up time moved earlier in the day. Although in humans there are no studies on the effects of ketogenic diet on circadian rhythm, there are studies reporting an improvement of sleep structure, which is a direct expression of circadian rhythm. Thus, a chronotype-driven treatment approach could at least potentiate the efficacy of anti-obesity treatments.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Funding Sources

No funding sources to declare.

Author Contributions

Giovanna Muscogiuri was in charge of the concept and writing and reviewing of this manuscript.

References

1 Horne JA, Ostberg O. A self-assessment questionnaire to determine morningness-eveningness in human circadian rhythms. Int J Chronobiol. 1976;4(2):97–110.
2 Muscogiuri G, Barrea L, Aprano S, Framondi L, Di Matteo R, Laudisio D, et al. Chronotype and adherence to the mediterranean diet in obesity: results from the opera prevention project. Nutrients. 2020;12(5):1354.
3 Sun X, Gustat J, Bertisch SM, Redline S, Bazzano L. The association between sleep chronotype and obesity among black and white participants of the Bogalusa Heart Study. Chronobiology Int. 2020;37(1):123–34.
4 Turkoglu S, Cetin FH. The relationship between chronotype and obesity in children and adolescent with attention deficit hyperactivity disorder. Chronobiology Int. 2019;36(8):1138–47.
5 Castellucci B, Barrea L, Laudisio D, Aprano S, Pugliese G, Savastano S, et al. Improving sleep disturbances in obesity by nutritional strategies: review of current evidence and practical guide. Int J Food Sci Nutr. 2021;72(5):579–91.
6 Holler Y, Gudjonsdottir BE, Valgeirsdottir SK, Heimisson GT. The effect of age and chronotype on seasonality, sleep problems, and mood. Psychiatry Res. 2021;297:113722.
7 Muscogiuri G, Barrea L, Annunziata G, Di Somma C, Laudisio D, Colao A, et al. Obesity and sleep disturbance: the chicken or the egg? Crit Rev Food Sci Nutr. 2019;59(13):2158–65.
8 Muscogiuri G, Barrea L, Aprano S, Framondi L, Di Matteo R, Laudisio D, et al. Sleep quality in obesity: does adherence to the mediterranean diet matter? Nutrients. 2020;12(5):1364.
9 Reutrakul S, Hood MM, Crowley SJ, Morgan MK, Teodori M, Knutson KL, et al. Chronotype is independently associated with glycemic control in type 2 diabetes. Diabetes Care. 2013;36(9):2523–9.
10 Merikanto I, Lahti T, Puolijoki H, Vanhala M, Peltonen M, Laatikainen T, et al. Associations of chronotype and sleep with cardiovascular diseases and type 2 diabetes. Chronobiology Int. 2013;30(4):470–7.
11 Hurley S, Goldberg D, Von Behren J, Clague DeHart J, Wang S, Reynolds P. Chronotype and postmenopausal breast cancer risk among women in the California Teachers Study. Chronobiology Int. 2019;36(11):1504–14.
12 Teixeira GP, Balieiro LCT, Gontijo CA, Fahmy WM, Maia YCP, Crispim CA. The association between chronotype, food craving and weight gain in pregnant women. J Hum Nutr Diet. 2020;33(3):342–50.
13 Muscogiuri G, Barrea L, Laudisio D, Pugliese G, Aprano S, Framondi L, et al. The opera prevention project. Int J Food Sci Nutr. 2021;72(1):1–3.

14 Patterson F, Malone SK, Lozano A, Grandner MA, Hanlon AL. Smoking, screen-based sedentary behavior, and diet associated with habitual sleep duration and chronotype: data from the UK Biobank. Ann Behav Med. 2016;50(5):715–26.
15 Kanerva N, Kronholm E, Partonen T, Ovaskainen ML, Kaartinen NE, Konttinen H, et al. Tendency toward eveningness is associated with unhealthy dietary habits. Chronobiology Int. 2012;29(7):920–7.
16 Maukonen M, Kanerva N, Partonen T, Kronholm E, Konttinen H, Wennman H, et al. The associations between chronotype, a healthy diet and obesity. Chronobiology Int. 2016;33(8):972–81.
17 Putilov AA, Poluektov MG, Dorokhov VB. Evening chronotype, late weekend sleep times and social jetlag as possible causes of sleep curtailment after maintaining perennial DST: ain't they as black as they are painted? Chronobiology Int. 2020;37(1):82–100.
18 Barrea L, Pugliese G, Framondi L, Di Matteo R, Laudisio D, Savastano S, et al. Does SARS-Cov-2 threaten our dreams? Effect of quarantine on sleep quality and body mass index. J Transl Med. 2020;18(1):318.
19 Spiegel K, Tasali E, Penev P, Cauter EV. Brief communication: sleep curtailment in healthy young men is associated with decreased leptin levels, elevated ghrelin levels, and increased hunger and appetite. Ann Intern Med. 2004;141(11):846–50.
20 Taheri S, Lin L, Austin D, Young T, Mignot E. Short sleep duration is associated with reduced leptin, elevated ghrelin, and increased body mass index. PLoS Med. 2004;1(3):e62.
21 Chaput JP, Despres JP, Bouchard C, Tremblay A. Short sleep duration is associated with reduced leptin levels and increased adiposity: results from the Quebec family study. Obesity (Silver Spring). 2007;15(1):253–61.
22 Spiegel K, Leproult R, L'Hermite-Baleriaux M, Copinschi G, Penev PD, Van Cauter E. Leptin levels are dependent on sleep duration: relationships with sympathovagal balance, carbohydrate regulation, cortisol, and thyrotropin. J Clin Endocrinol Metab. 2004;89(11):5762–71.
23 Patel SR, Malhotra A, White DP, Gottlieb DJ, Hu FB. Association between reduced sleep and weight gain in women. Am J Epidemiol. 2006;164(10):947–54.
24 Reilly JJ, Armstrong J, Dorosty AR, Emmett PM, Ness A, Rogers I, et al. Early life risk factors for obesity in childhood: cohort study. BMJ. 2005;330(7504):1357.
25 von Kries R, Toschke AM, Wurmser H, Sauerwald T, Koletzko B. Reduced risk for overweight and obesity in 5- and 6-y-old children by duration of sleep: a cross-sectional study. Int J Obes. 2002;26(5):710–6.
26 Sivak M. Sleeping more as a way to lose weight. Obes Rev. 2006;7(3):295–6.
27 Dinges DF, Pack F, Williams K, Gillen KA, Powell JW, Ott GE, et al. Cumulative sleepiness, mood disturbance, and psychomotor vigilance performance decrements during a week of sleep restricted to 4-5 hours per night. Sleep. 1997;20(4):267–77.
28 Patel SR, Malhotra A, Gottlieb DJ, White DP, Hu FB. Correlates of long sleep duration. Sleep. 2006;29(7):881–9.
29 Poggiogalle E, Jamshed H, Peterson CM. Circadian regulation of glucose, lipid, and energy metabolism in humans. Metabolism. 2018;84:11–27.
30 Anothaisintawee T, Lertrattananon D, Thamakaison S, Knutson KL, Thakkinstian A, Reutrakul S. Later chronotype is associated with higher hemoglobin A1c in prediabetes patients. Chronobiology Int. 2017;34(3):393–402.
31 Muscogiuri G, Barrea L, Aprano S, Framondi L, Di Matteo R, Altieri B, et al. Chronotype and cardio metabolic health in obesity: does nutrition matter? Int J Food Sci Nutr. 2021;72(7):892–900.
32 Barrea L, Vetrani C, Altieri B, Verde L, Savastano S, Colao A, et al. The importance of being a "lark" in post-menopausal women with obesity: a ploy to prevent type 2 diabetes mellitus? Nutrients. 2021;13(11):3762.
33 Dockray S, Steptoe A. Chronotype and diurnal cortisol profile in working women: differences between work and leisure days. Psychoneuroendocrinology. 2011;36(5):649–55.
34 Kudielka BM, Federenko IS, Hellhammer DH, Wust S. Morningness and eveningness: the free cortisol rise after awakening in "early birds" and "night owls". Biol Psychol. 2006;72(2):141–6.
35 Abraham SB, Rubino D, Sinaii N, Ramsey S, Nieman LK. Cortisol, obesity, and the metabolic syndrome: a cross-sectional study of obese subjects and review of the literature. Obesity (Silver Spring). 2013;21(1):E105–17.
36 Baudrand R, Vaidya A. Cortisol dysregulation in obesity-related metabolic disorders. Curr Opin Endocrinol Diabetes Obes. 2015;22(3):143–9.
37 Turek FW, Joshu C, Kohsaka A, Lin E, Ivanova G, McDearmon E, et al. Obesity and metabolic syndrome in circadian Clock mutant mice. Science. 2005;308(5724):1043–5.
38 Garaulet M, Esteban Tardido A, Lee YC, Smith CE, Parnell LD, Ordovas JM. SIRT1 and CLOCK 3111T> C combined genotype is associated with evening preference and weight loss resistance in a behavioral therapy treatment for obesity. Int J Obes. 2012;36(11):1436–41.
39 Scott EM, Carter AM, Grant PJ. Association between polymorphisms in the Clock gene, obesity and the metabolic syndrome in man. Int J Obes. 2008;32(4):658–62.
40 Woon PY, Kaisaki PJ, Braganca J, Bihoreau MT, Levy JC, Farrall M, et al. Aryl hydrocarbon receptor nuclear translocator-like (BMAL1) is associated with susceptibility to hypertension and type 2 diabetes. Proc Natl Acad Sci U S A. 2007;104(36):14412–7.
41 Vitale JA, Roveda E, Montaruli A, Galasso L, Weydahl A, Caumo A, et al. Chronotype influences activity circadian rhythm and sleep: differences in sleep quality between weekdays and weekend. Chronobiology Int. 2015;32(3):405–15.
42 Pugliese G, Barrea L, Laudisio D, Salzano C, Aprano S, Colao A, et al. Sleep apnea, obesity, and disturbed glucose homeostasis: epidemiologic evidence, biologic insights, and therapeutic strategies. Curr Obes Rep. 2020;9(1):30–8.
43 Dickerman BA, Markt SC, Koskenvuo M, Hublin C, Pukkala E, Mucci LA, et al. Sleep disruption, chronotype, shift work, and prostate cancer risk and mortality: a 30-year prospective cohort study of Finnish twins. Cancer Causes Control. 2016;27(11):1361–70.
44 Hahm BJ, Jo B, Dhabhar FS, Palesh O, Aldridge-Gerry A, Bajestan SN, et al. Bedtime misalignment and progression of breast cancer. Chronobiology Int. 2014;31(2):214–21.
45 Lee KM, Jung DY, Hwang H, Kim WH, Lee JY, Kim TY, et al. Late chronotypes are associated with neoadjuvant chemotherapy-induced nausea and vomiting in women with breast cancer. Chronobiology Int. 2017;34(4):480–91.
46 Lozano-Lorca M, Olmedo-Requena R, Vega-Galindo MV, Vazquez-Alonso F, Jimenez-Pacheco A, Salcedo-Bellido I, et al. Night shift work, chronotype, sleep duration, and prostate cancer risk: CAPLIFE study. Int J Environ Res Public Health. 2020;17(17):6300.
47 Son KL, Jung D, Lee KM, Hwang H, Lee J, Kim TY. Morning chronotype is a protective factor against chemotherapy-induced hot flashes in premenopausal women with breast cancer. Support Care Cancer. 2020;28(3):1351–8.
48 Sun X, Ye D, Jiang M, Qian Y, Mao Y. Genetically proxied morning chronotype was associated with a reduced risk of prostate cancer. Sleep. 2021;44(10):zsab104.
49 Von Behren J, Hurley S, Goldberg D, Clague DeHart J, Wang SS, Reynolds P. Chronotype and risk of post-menopausal endometrial cancer in the California Teachers Study. Chronobiology Int. 2021;38(8):1151–61.
50 group IMV. Carcinogenicity of night shift work. Lancet Oncol. 2019;20(8):1058–9.
51 Hudec M, Dankova P, Solc R, Bettazova N, Cerna M. Epigenetic regulation of circadian rhythm and its possible role in diabetes mellitus. Int J Mol Sci. 2020;21(8):3005.
52 Shafi AA, Knudsen KE. Cancer and the circadian clock. Cancer Res. 2019;79(15):3806–14.
53 Bhatti P, Mirick DK, Davis S. The impact of chronotype on melatonin levels among shift workers. Occup Environ Med. 2014;71(3):195–200.
54 Bhattacharya S, Patel KK, Dehari D, Agrawal AK, Singh S. Melatonin and its ubiquitous anticancer effects. Mol Cel Biochem. 2019;462(1–2):133–55.
55 Talib WH. Melatonin and cancer hallmarks. Molecules. 2018;23(3):518.

56 Kolak A, Kaminska M, Sygit K, Budny A, Surdyka D, Kukielka-Budny B, et al. Primary and secondary prevention of breast cancer. Ann Agric Environ Med. 2017;24(4):549–53.
57 Engin A. Obesity-associated breast cancer: analysis of risk factors. Adv Exp Med Biol. 2017;960:571–606.
58 Surmacz E. Leptin and adiponectin: emerging therapeutic targets in breast cancer. J Mammary Gland Biol Neoplasia. 2013;18(3–4):321–32.
59 Barbieri I, Pensa S, Pannellini T, Quaglino E, Maritano D, Demaria M, et al. Constitutively active Stat3 enhances neu-mediated migration and metastasis in mammary tumors via upregulation of Cten. Cancer Res. 2010;70(6):2558–67.
60 Lee JO, Kim N, Lee HJ, Lee YW, Kim SJ, Park SH, et al. Resistin, a fat-derived secretory factor, promotes metastasis of MDA-MB-231 human breast cancer cells through ERM activation. Sci Rep. 2016;6(1):18923.
61 Wang CH, Wang PJ, Hsieh YC, Lo S, Lee YC, Chen YC, et al. Resistin facilitates breast cancer progression via TLR4-mediated induction of mesenchymal phenotypes and stemness properties. Oncogene. 2018;37(5):589–600.
62 Yu H, Lee H, Herrmann A, Buettner R, Jove R. Revisiting STAT3 signalling in cancer: new and unexpected biological functions. Nat Rev Cancer. 2014;14(11):736–46.
63 Grossmann ME, Nkhata KJ, Mizuno NK, Ray A, Cleary MP. Effects of adiponectin on breast cancer cell growth and signaling. Br J Cancer. 2008;98(2):370–9.
64 Taliaferro-Smith L, Nagalingam A, Knight BB, Oberlick E, Saxena NK, Sharma D. Integral role of PTP1B in adiponectin-mediated inhibition of oncogenic actions of leptin in breast carcinogenesis. Neoplasia. 2013;15(1):23–IN11.
65 Taliaferro-Smith L, Nagalingam A, Zhong D, Zhou W, Saxena NK, Sharma D. LKB1 is required for adiponectin-mediated modulation of AMPK-S6K axis and inhibition of migration and invasion of breast cancer cells. Oncogene. 2009;28(29):2621–33.
66 Gunter MJ, Wang T, Cushman M, Xue X, Wassertheil-Smoller S, Strickler HD, et al. Circulating adipokines and inflammatory markers and postmenopausal breast cancer risk. J Natl Cancer Inst. 2015;107(9):djv169.
67 Rojas K, Stuckey A. Breast cancer epidemiology and risk factors. Clin Obstet Gynecol. 2016;59(4):651–72.
68 Litwin MS, Tan HJ. The diagnosis and treatment of prostate cancer: a review. JAMA. 2017;317(24):2532–42.
69 Bandini M, Gandaglia G, Briganti A. Obesity and prostate cancer. Curr Opin Urol. 2017;27(5):415–21.
70 Gallagher EJ, LeRoith D. The proliferating role of insulin and insulin-like growth factors in cancer. Trends Endocrinol Metab. 2010;21(10):610–8.
71 Lane BR, Stephenson AJ, Magi-Galluzzi C, Lakin MM, Klein EA. Low testosterone and risk of biochemical recurrence and poorly differentiated prostate cancer at radical prostatectomy. Urology. 2008;72(6):1240–5.
72 Booth A, Magnuson A, Fouts J, Foster M. Adipose tissue, obesity and adipokines: role in cancer promotion. Horm Mol Biol Clin Investig. 2015;21(1):57–74.
73 Grossmann ME, Mizuno NK, Bonorden MJL, Ray A, Sokolchik I, Narasimhan ML. Role of the adiponectin leptin ratio in prostate cancer. Oncol Res. 2009;18(5):269–77.
74 Liu Q, Xu Z, Mao S, Chen W, Zeng R, Zhou S, et al. Effect of hypoxia on hypoxia inducible factor-1α, insulin-like growth factor I and vascular endothelial growth factor expression in hepatocellular carcinoma HepG2 cells. Oncol Lett. 2015;9(3):1142–8.
75 Calle EE, Rodriguez C, Walker-Thurmond K, Thun MJ. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med. 2003;348(17):1625–38.
76 Akhmedkhanov A, Zeleniuch-Jacquotte A, Toniolo P. Role of exogenous and endogenous hormones in endometrial cancer: review of the evidence and research perspectives. Ann N Y Acad Sci. 2001;943(1):296–315.