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EDITORIAL

Cancer and rhythm

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In a recent editorial comment, Denise Duboule [1] emphasized that ''animal development is, in fact, nothing but time.'' In this issue of *Cancer Causes and Control*, several papers will substantiate that not only developmental, but also neoplastic processes may be linked to what Duboule [1] and Halberg [2] referred to as 'chronomics': timing and rhythm. Moreover, there is reason to believe that timing and rhythm may have been underappreciated in current therapeutic settings [3]. The papers in this issue of *Cancer Causes and Control* are from leading researchers in the field of cancer and body rhythms. Each one addresses a specific aspect of the topic, and their work is cited below in this overview editorial.

Evidence from observational studies is growing [4] that the disturbance of body rhythms, in particular, circadian disruption e.g., shift work [5–8] or chronic jet-lag [9–12] contribute significantly to the development of breast cancer. Figure 1 compares the relative impact of rhythm disturbances to other exposures of significance in breast tumor development [13]. Reproductive risk factors such as parity and age at first birth, age at menarche, and age at menopause each confer a change in risk of roughly 20–30%. Only family history in a first degree confers a relative risk comparable in magnitude to that of female flight attendants. Unlike for other cancers for which primary risk factors have been identified (e.g., smoking and lung cancer risk), to date, no single environmental risk factor has been identified that can account for a major proportion of breast cancers, the incidence of which is still rising. Thus, there is a need for continued, vigorous search of breast cancer risk factors. Disruption of circadian rhythms, which can be caused by a wide variety of factors, may play an important role, not only for breast—but also other cancers, but results are still premature.

Disruption of clock gene function may increase cancer risk: In mice, clock genes stabilize the genome and help maintain important repair mechanisms such as the apoptosis of damaged cells [14]. Per-2 gene deprived mice lack a circadian rhythm [15] and have been shown to develop cancer rapidly and spontaneously. The difference between wild type and rhythm-deprived mice was found to be most striking after exposure to ionizing radiation. In suprachiasmatic nuclei (SCN) ablated mice, disruption of circadian rhythms was associated with accelerated growth of

Dedication This special issue of CCC is dedicated to Gunther Hildebrandt (Marburg, Germany) and Franz Halberg (Minnesota, USA), two great pioneers of Chronobiology.

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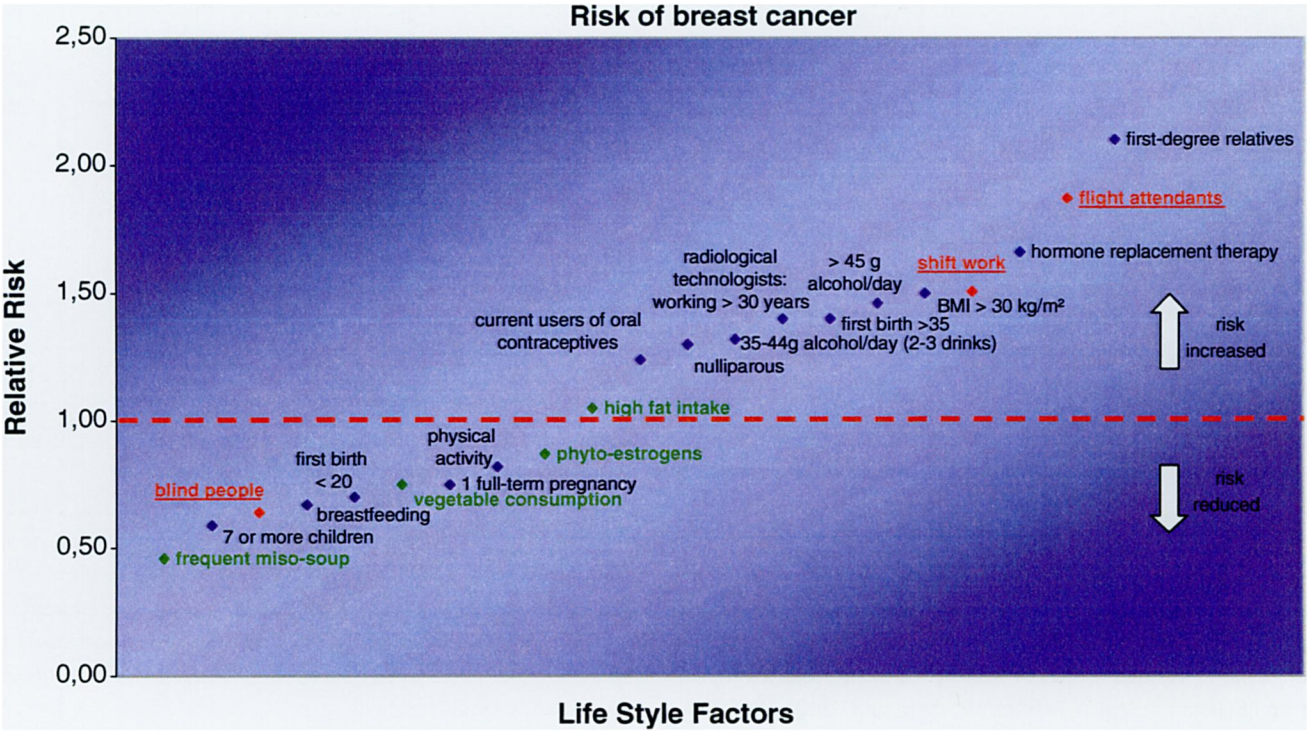

Fig. 1 Risk and beneficial factors influencing relative breast cancer risks have been extracted from the literature (see Electronic Supplementary Material). Possible chronobiological factors are marked in red, nutritional factors in green, all others in blue. The red line at 1.00 indicates the breast cancer risk of the control cohort documented in the studies. Higher values e.g. in shift workers and flight attendants correspond to an increased risk. Some factors are known to decrease the risk of breast cancer, e.g. breastfeeding, the number of pregnancies and phytoestrogens contained in vegetables and miso soup

malignant tumors, suggesting that the host circadian clock may play an important role in endogenous control of tumor progression [16, 17].

A similar amplification of cancer promotion through disturbed body rhythms could also be inferred from Fig. 1. A recent meta-analysis of breast cancer risk in flight attendants and shift working women has estimated that the overall relative risk is about 1.5 [18]. There is variability among these studies in what constitutes shift work and of whom the comparison group is comprised, so more must be learned about the impact of occupational circadian rhythm disturbance and risk. In particular, there may be possible interactions with other exposures such as cosmic radiation in the flight attendants.

In animal studies, chronic jet lag suppressed the rhythm in clock gene expression in normal liver and in tumors [19, 20]. Prolonged exposure to constant light promoted growth of transplantable tumors in rats [21, 22] and mice [23], whereas melatonin and rest-activity rhythms were suppressed.

Cancer growth on the other hand may also disturb body rhythms: for example, rhythms of cancer cells degenerate from those of their host organism [24–26]. Chen et al. [27] showed deregulation of clock genes in tumor cells compared to normal cells in breast cancers.

It has also been argued that rhythm disturbance is not a carcinogenic effect in itself [28]: Light at night induces a decrease of plasma melatonin levels [4, 29] via specialized retinal photoreceptors that were only recently discovered [30–32]. Since both blind people [33–36] as well as workers in photographic laboratories [37] were reported to have lower breast cancer incidence rates than the general population, melatonin has been implicated. However, among cancer patients, not only changes in melatonin levels, but also changes in their circadian rhythms were found, in some cases independent of their melatonin levels [38, 39]. Untreated breast and prostate cancer patients, on the other hand, were found to show tumor-size dependent depressions of the circadian amplitude of circulating melatonin, which was accompanied by parallel neuroendocrine disturbances involving particularly prolactin and TSH [40]. Also colorectal cancer patients [39, 41] as well as patients with lung and stomach cancer [42] had lower levels of melatonin in plasma resp. 6-sulfatoxymelatonin in urine than healthy control subjects, suggesting a possible link between low melatonin levels and the enhanced

development of cancer in humans. Overall, a strong interaction between rhythm disturbances and melatonin levels appear most likely: a recent study demonstrates the interplay between melatonin levels, rhythm disturbances and tumor growth: blood from human donors collected during a normal night was able to suppress proliferative activity in rats xenografted with human breast cancer [43]. Blood collected during the day or after a white light exposure during the night did not. In sum, only subjects that had not been exposed to light at night produced enough melatonin to suppress proliferative cell growth in this animal model. So, melatonin may also be beneficial in cancer treatment if administered at chronobiologically determined optimal times of the day [44]: according to this study, evening administration stabilized quality of life and prevented cancer-related cachexia. Significantly less patients showed a progressive disease in the melatonin group. Further evidence [45] supports the notion that melatonin is beneficial in human cancer treatment regardless of the timing of its administration. Other studies, finally, suggest melatonin as a possible remedy against jet-lag: Manfredini et al. [46] and Cardinali et al. [47] administered melatonin to athletes after transmeridian flights. Cardinali's athletes displayed fewer jet lag symptoms and coped better than those of Manfredini. The former group received an additional 'Zeitgeber' training, which appears to increase melatonin's efficacy. With growing data, we therefore argue that circulating melatonin levels may be only one aspect of the cancer-protective effects of stable biological rhythms. While rhythm disturbances are likely to aggravate tumor growth, the use of well chosen ''Zeitgebers'' could be of additional value to prevent tumors or to support tumor therapy.

''Zeitgebers'', as defined by Aschoff in the 1960s [48], are cues, which help organisms to establish and stabilize their biologic rhythms. Such cues may be parameters like morning light, which indicates the beginning of the day. Temperature changes and meals, as well as the administration of drugs at a certain phase of the circadian cycle are other examples of such ''Zeitgebers''.

''Zeitgebers'' have also been used as therapeutic elements is chrono-chemotherapy [49–51]. Chrono-chemotherapy implies drug administration to cancer patients at what is considered 'the right time of the day', following the 'Kairos' principle.[1] However, although such timing has been shown to successfully reduce the adverse effects of toxic agents [52], it has so far only rarely resulted in an increase of survival rates when compared to conventional, constant-rate infusion [53]. Thus, and because chemotherapy in itself reduces the amplitude of body rhythms [54–56], it might not work outside the framework of an accompanying ''rhythm therapy'', which is yet to be established in oncology.

By using several ''Zeitgebers'' in the right order, it is possible to develop novel rhythm therapies. What are the basic elements of such a rhythm therapy? Klages [57] distinguishes between 'tact' and 'rhythm': 'tact' refers to identical things happening during identical periods, whereas 'rhythm' refers to similar things happening during similar periods. Today, it has been established that biological rhythms are not rigid but flexible; thus, a rhythm therapy should also take flexibility into account. For example, the circadian phase of a patient could be determined prior to intervention and be considered when designing a patient's treatment regimen. Determining whether the patient is an ''owl'' or a ''lark'' (evening/morning type [2, 50, 58] could thus lead to a better adaptation of the therapy.

To date, ''Zeitgeber'' training has been applied in a variety of diseases. For example, light at the right time of the day seems to substantially improve the condition of patients suffering from seasonal affective disorder [59]; modification of the sleep pattern intended to reset the circadian clock has been successfully used to improve psychiatric depression [60]; a rhythm therapy has been developed for patients following stroke (http://www.viewzone.com/rhythm_therapy.html). We too, have recently shown that both the number of accidents as well as quality of sleep in stressed construction workers were significantly improved by applying a rhythm therapy [61]. This involved not only the introduction of additional ''Zeitgebers'' (e.g. working breaks in a pattern adopted from the human basic rest and activity cycle), but also the enhancement of body rhythms by resonance phenomena and by coordinating different body rhythms through art therapy [62, 63]. We further observed that excitation of the biological system with ultradian short period rhythms increases the amplitude of its long period rhythms, thereby enlarging the circadian cycle of heart rate and heart rate variability [61], both of which are connected to sleep quality.

In sum, the elements of an optimal rhythm therapy should incorporate:

- Use of several ''Zeitgebers'' to complement each other instead of a simple Zeitgeber at a time;
- the use of ultradian short period ''Zeitgebers'' (to enhance long period circadian rhythms by excitation, coupling and resonance);
- measures to coordinate various body rhythms;
- flexible and individualized rhythms instead of metronomic periods
- Kairos instead of Chronos (right timing instead of arbitrarily set timing)

[1] Kairos (καιρος) is the Greek word for the right time in contrast to Chronos (χρονος), the term for time in general.

We suggest that maintenance of a strong circadian rhythm in everyday life [64] and the use of rhythm therapy when disease occurs [65], may not only help to substantially reduce breast cancer incidence and mortality in industrialized countries, but, more generally, will also support the introduction of new avenues in the prevention and treatment of cancer [3].

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