

Article

Tele-Monitoring of Cancer Patients' Rhythms during Daily Life Identifies Actionable Determinants of Circadian and Sleep Disruption.

Francis Lévi ^{1,2,3,*}, Sandra Komarzynski ^{1,2}, Qi Huang ^{1,4}, Teresa Young ⁵, Yeng Ang ^{6,7},
Claire Fuller ⁸, Matei Bolborea ¹, Julia Brettschneider ⁴, Joanna Fursse ¹, Bärbel Finkenstädt ^{2,4},
David Pollard White ^{9,10} and Pasquale Innominato ^{1,2,8}

- ¹ Cancer Chronotherapy Team, Warwick Medical School, Coventry CV4 7AL, UK; S.Komarzynski@warwick.ac.uk (S.K.); Q.Huang.6@warwick.ac.uk (Q.H.); M.Bolborea@warwick.ac.uk (M.B.); Joanna.fursse@nhs.net (J.F.); Pasquale.Innominato@wales.nhs.uk (P.I.)
 - ² European Laboratory U935, Institut National de la Santé et de la Recherche Médicale (INSERM), and Paris-Saclay University, Villejuif 94801, France; B.F.Finkenstadt@warwick.ac.uk
 - ³ Hepato-biliary Centre, Paul Brousse Hospital, Assistance Publique Hôpitaux de Paris (AP-HP), Villejuif 94800, France
 - ⁴ Department of Statistics, University of Warwick, Coventry CV4 7AL, UK; Julia.Brettschneider@warwick.ac.uk
 - ⁵ Mount Vernon Cancer Centre, East and North Hertfordshire NHS Trust, Northwood, Middlesex HA6 2RN, UK; Teresa.young2@nhs.net
 - ⁶ Salford Royal NHS Foundation Trust, Salford M6 8HD, UK; Yeng.Ang@srft.nhs.uk
 - ⁷ Gastrointestinal Sciences, Division of Diabetes, Endocrinology and Gastroenterology, Faculty of Biology, Medicine and Health, University of Manchester, Manchester M13 9PL, UK
 - ⁸ North Wales Cancer Treatment Centre, Ysbyty Gwynedd, Betsi Cadwaladr University Health Board, Bangor LL57 2PW, UK; Claire.Fuller2@wales.nhs.uk
 - ⁹ Division of Sleep and Circadian Disorders, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02130, USA; dpwhite@partners.org
 - ¹⁰ Philips Respironics, Murrysville, PA 15668, USA
- * Correspondence: F.Levi@warwick.ac.uk; Tel.: +44-2476-575-132

Supplementary

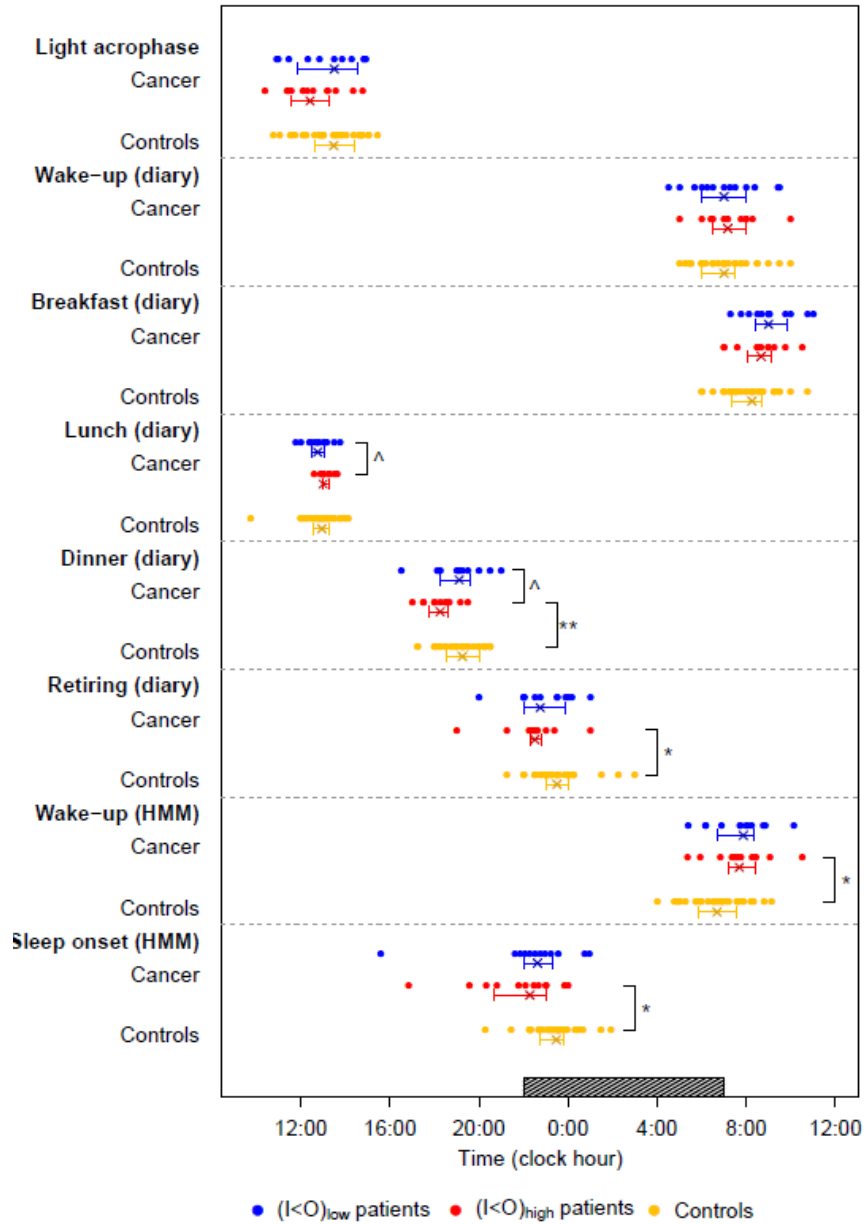


Figure S1. Environmental synchronizing signals. Median, interquartiles, and individual median timings of each environmental signal according to either I < O cancer group (11 to 13 participants for each signal) or control group (31 to 33 participants).

Table S1. Sex or age effects on the rest-activity and chest surface temperature circadian parameters, synchronization signals, cortisol rhythm, and DLMO in the controls. When not specified the data are presented as Number of subjects (%).

	Age < 40 years	Age ≥ 40 years	Male	Female
Rest-activity circadian rhythm	N=18	N=15	N=15	N=18
<i>I<O over study week (%)</i>		p=0.01*		p=0.98
Median [Q1, Q3]	99.7 [98.9, 100.0]	98.3 [97.5, 99.4]	99.2 [98.4, 99.8]	99.1 [98.4, 99.8]
Range	98.0 - 100.0	95.0 - 100.0	95.0 - 100.0	95.5 - 100.0
<i>Median of moderate-to-high activity (acc/min)</i>		p=0.22		p=0.41
Median [Q1, Q3]	172.7 [162.5, 185.8]	185.3 [172.9, 199.6]	174.7 [158.1, 194.4]	178.6 [169.2, 190.9]
Range	132.5 - 208.5	142.7 - 210.0	132.5 - 208.5	149.7 - 210.0
<i>Circadian amplitude (acc/min)</i>		p=0.17		p=0.27
Median [Q1, Q3]	61.1 [53.1, 69.1]	67.5 [63.0, 78.1]	62.5 [54.8, 80.1]	66.5 [54.6, 71.4]
Range	39.3 - 105.2	39.5 - 101.5	45.6 - 105.2	39.3 - 82.2
<i>Circadian acrophase (clock time)</i>		p=0.01*		p=0.71
Median [Q1, Q3]	15:07 [14:11, 16:14]	14:00 [12:29, 14:50]	14:33 [12:48, 15:23]	14:31 [13:57, 15:50]
Range	11:59 - 17:10	11:43 - 16:01	11:59 - 17:10	11:43 - 16:49
<i>P1-1</i>		p=0.0009***		p=0.63
Median [Q1, Q3]	0.97 [0.97, 0.98]	0.96 [0.94, 0.97]	0.97 [0.96, 0.98]	0.97 [0.96, 0.97]
Range	0.96 - 0.99	0.93 - 0.98	0.94 - 0.99	0.93 - 0.98
<i>r24</i>		p=0.30		p=0.39
Median [Q1, Q3]	0.36 [0.30, 0.41]	0.39 [0.32, 0.45]	0.39 [0.29, 0.42]	0.34 [0.33, 0.44]
Range	0.09 - 0.63	0.20 - 0.55	0.17 - 0.63	0.09 - 0.47
<i>Rhythm Index</i>		p=0.23		p=0.21
Median [Q1, Q3]	0.79 [0.74, 0.83]	0.74 [0.58, 0.80]	0.79 [0.74, 0.84]	0.77 [0.63, 0.81]
Range	0.47 - 0.90	0.48 - 0.92	0.57 - 0.92	0.47 - 0.90
<i>Rest duration (hours)</i>		p=0.56		p=0.85
Median [Q1, Q3]	8.0 [7.4, 8.8]	8.3 [7.5, 9.4]	8.1 [7.7, 8.9]	7.9 [7.3, 8.9]
Range	7.1 - 12.4	5.3 - 12.9	6.8 - 12.9	5.3 - 12.4

<i>Center-of-rest time (clock time)</i>		p=0.01*		p=0.96
Median [Q1, Q3]	03:22 [02:41, 03:47]	02:20 [01:48, 03:08]	03:00 [01:52, 03:22]	03:08 [02:24, 03:29]
Range	01:20 - 06:25	01:10 - 03:50	01:10 - 06:25	01:20 - 05:20
Chest surface temperature circadian rhythm	N=9	N=12	N=10	N=11
<i>Circadian amplitude (°C) - SR</i>		p=0.04*		p=0.37
Median [Q1, Q3]	0.7 [0.5, 0.8]	1.1 [0.6, 1.3]	1.0 [0.7, 1.3]	0.7 [0.5, 0.9]
Range	0.4 - 1.0	0.2 - 2.1	0.5 - 1.5	0.2 - 2.1
<i>Circadian acrophase (clock time) - SR</i>		p=0.35		p=0.07^
Median [Q1, Q3]	02:16 [00:59, 03:55]	02:51 [01:45, 04:04]	02:03 [00:27, 02:28]	03:55 [02:33, 04:51]
Range	23:35 - 05:23	00:06 - 15:49	00:06 - 04:46	23:35 - 15:49
<i>Physiologic chest surface temperature</i>		p=1		p=1
Yes	9 (100)	11 (91.7)	10 (100)	10 (90.9)
No	0 (0)	1 (8.3)	0 (0)	1 (9.1)
<i>Circadian mesor (°C) - cosinor</i>		p=0.58		p=0.0002***
Median [Q1, Q3]	34.9 [34.5, 35.3]	34.6 [34.2, 35.4]	34.5 [34.3, 34.6]	35.4 [34.9, 35.6]
Range	34.1 - 36.0	33.8 - 36.4	34.0 - 35.2	33.8 - 36.4
<i>Circadian amplitude (°C) - cosinor</i>		p=0.05*		p=0.64
Median [Q1, Q3]	0.9 [0.7, 1.0]	1.2 [1.0, 1.4]	1.2 [0.9, 1.4]	1.0 [0.8, 1.1]
Range	0.5 - 1.3	0.3 - 2.4	0.5 - 1.7	0.3 - 2.4
<i>Circadian acrophase (clock time) - cosinor</i>		p=0.17		p=0.75
Median [Q1, Q3]	03:10 [02:25, 04:50]	02:58 [02:17, 03:44]	02:22 [02:13, 03:25]	02:58 [02:17, 03:44]
Range	01:40 - 06:20	22:30 - 04:05	22:30 - 06:20	22:30 - 04:05
Synchronization signals	N=18	N=15	N=15	N=18
<i>Light acrophase (clock time)</i>		p=0.56		p=0.70
Median [Q1, Q3]	13:15 [12:23, 13:47]	13:30 [12:44, 14:39]	13:02 [12:45, 13:56]	13:33 [12:23, 14:34]
Range	11:32 - 15:02	10:46 - 15:26	10:46 - 15:02	11:02 - 15:26

Table S2. Comparison of rest-activity and chest surface temperature circadian parameters, synchronization signals, cortisol rhythm and DLMO between the (I<O>_{high}) patients and the controls older than 40 years. When not specified the data are presented as Number of subjects (%).

	Controls Age ≥ 40 years N=15	Cancer patients (I<O> _{high}) N=12
Rest-activity circadian rhythm		
<i>I<O over study week (%)</i>		p=0.15
Median [Q1, Q3]	98.3 [97.5, 99.4]	97.3 [96.5, 98.6]
Range	95.0 - 100.0	93.3 - 99.0
<i>Median of moderate-to-high activity (acc/min)</i>		p<0.0001****
Median [Q1, Q3]	185.3 [172.9, 199.6]	106.1 [86.6, 131.2]
Range	142.7 - 210.0	47.8 - 169.2
<i>Circadian amplitude (acc/min)</i>		p=0.37
Median [Q1, Q3]	67.5 [63.0, 78.1]	63.9 [59.9, 71.7]
Range	39.5 - 101.5	46.8 - 91.1
<i>Circadian acrophase (clock time)</i>		p=0.35
Median [Q1, Q3]	14:00 [12:29, 14:50]	13:13 [12:13, 14:25]
Range	11:43 - 16:01	10:20 - 16:36
<i>P1-1</i>		p=0.01*
Median [Q1, Q3]	0.96 [0.94, 0.97]	0.94 [0.93, 0.94]
Range	0.93 - 0.98	0.91 - 0.97
<i>r24</i>		p=0.54
Median [Q1, Q3]	0.39 [0.32, 0.45]	0.36 [0.33, 0.43]
Range	0.20 - 0.55	0.25 - 0.54
<i>Rhythm Index</i>		p=0.60
Median [Q1, Q3]	0.74 [0.58, 0.80]	0.70 [0.63, 0.76]
Range	0.48 - 0.92	0.54 - 0.79
<i>Rest duration (hours)</i>		p=0.62
Median [Q1, Q3]	8.3 [7.5, 9.4]	8.4 [7.5, 10.7]
Range	5.3 - 12.9	6.4 - 12.6
<i>Center-of-rest time (clock time)</i>		p=0.16
Median [Q1, Q3]	02:20 [01:48, 03:08]	03:05 [02:17, 03:50]
Range	01:10 - 03:50	00:55 - 06:50
Chest surface temperature circadian rhythm		
<i>Circadian amplitude (°C) - SR</i>		p=0.18
Median [Q1, Q3]	1.1 [0.6, 1.3]	0.9 [0.6, 1.1]
Range	0.2 - 2.1	0.3 - 1.4
<i>Circadian acrophase (clock time) - SR</i>		p=0.20
Median [Q1, Q3]	02:51 [01:45, 04:04]	01:33 [23:55, 03:09]
Range	00:06 - 15:49	20:17 - 08:44
<i>Physiologic chest surface temperature</i>		p=0.59
Yes	11 (91.7)	9 (81.8)
No	1 (8.3)	2 (18.2)
<i>Circadian mesor (°C) - cosinor</i>		p=0.27
Median [Q1, Q3]	34.6 [34.2, 35.4]	35.1 [34.9, 35.4]
Range	33.8 - 36.4	33.9 - 35.9
<i>Circadian amplitude (°C) - cosinor</i>		p=0.12
Median [Q1, Q3]	1.2 [1.0, 1.4]	1.0 [0.7, 1.1]
Range	0.3 - 2.4	0.5 - 1.5
<i>Circadian acrophase (clock time) - cosinor</i>		p=0.40
Median [Q1, Q3]	02:58 [02:17, 03:44]	03:10 [02:16, 04:03]
Range	22:30 - 04:05	18:50 - 04:40
Synchronization signals		
<i>Light acrophase (clock time)</i>		p=0.11
Median [Q1, Q3]	13:30 [12:44, 14:39]	12:24 [11:32, 13:17]
Range	10:46 - 15:26	10:23 - 14:46
<i>Median wake-up time (clock time) - diary</i>		p=0.06^
Median [Q1, Q3]	06:10 [05:45, 07:00]	07:10 [06:27, 08:00]
Range	05:00 - 07:45	05:00 - 10:00
<i>Median breakfast time (clock time) - diary</i>		p=0.15

Median [Q1, Q3]	08:00 [07:22, 08:34]	08:40 [08:02, 09:07]
Range	06:30 - 09:30	07:00 - 10:30
Median lunch time (clock time) - diary	p=0.13	
Median [Q1, Q3]	12:52 [12:34, 13:11]	13:00 [13:00, 13:15]
Range	09:45 - 13:45	12:35 - 13:37
Median dinner time (clock time) - diary	p=0.02*	
Median [Q1, Q3]	19:00 [18:30, 19:30]	18:15 [17:45, 18:35]
Range	17:15 - 20:15	17:00 - 19:30
Median retiring time (clock time) - diary	p=0.20	
Median [Q1, Q3]	23:00 [22:38, 23:42]	22:30 [22:17, 22:48]
Range	21:15 - 00:15	19:00 - 01:00
Median wake-up time (clock time) - HMM	p=0.008**	
Median [Q1, Q3]	06:31 [05:30, 07:16]	07:41 [07:13, 08:25]
Range	04:01 - 07:53	05:22 - 10:30
Median sleep onset (clock time) - HMM	p=0.10^	
Median [Q1, Q3]	22:52 [22:30, 23:28]	22:16 [20:41, 23:00]
Range	20:16 - 00:30	16:50 - 00:00
Salivary cortisol circadian rhythm	N=13	N=7
Circadian mesor (mol/L)	p=0.18	
Median [Q1, Q3]	4.4 [3.3, 5.2]	5.6 [4.4, 7.0]
Range	3.1 - 7.2	3.1 - 9.4
Circadian amplitude (mol/L)	p=0.01*	
Median [Q1, Q3]	3.3 [2.8, 3.9]	5.2 [3.9, 6.3]
Range	1.9 - 5.5	3.4 - 6.5
Circadian acrophase (clock time)	p=0.31	
Median [Q1, Q3]	08:47 [08:13, 09:09]	07:53 [07:11, 09:11]
Range	05:27 - 11:39	06:49 - 10:09
Dim Light Melatonin Onset	N=10	N=7
DLMO (clock time)	p=0.09^	
Median [Q1, Q3]	20:30 [19:21, 21:12]	21:44 [20:55, 22:16]
Range	17:22 - 21:33	18:23 - 23:32

Abbreviations: SR = Spectrum Resampling; HMM = Hidden Markov Model; DLMO = Dim Light Melatonin Onset. Comparisons between controls aged 40 years or more and cancer patients with (I<O)_{high} were done with two-tailed Welch's t-tests for continuous variables and Fisher's exact test for categorical variables. The corresponding p-values are shown for each parameter as follows: ****p<0.0001; ** 0.001< p ≤0.01; * 0.01< p ≤0.05; ^ 0.05< p ≤0.1.