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Short Report:

Cyclic patterns of incidence rate for skin malignant melanoma: association with heliogeophysical activity*

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Abstract: Background: Our previous studies revealed cyclicity in the incidence rate of skin malignant melanoma (SMM; ICD9, Dx:172) in the Czech Republic (period T=7.50~7.63 years), UK (T=11.00 years) and Bulgaria (T=12.20 years). Incidences compared with the sunspot index Rz (lag-period dT=+2, +4, +6, +10 or +12 years) have indicated that maximal rates are most likely to appear on descending slopes of the 11-year solar cycle, i.e., out of phase. We summarized and explored more deeply these cyclic variations and discussed their possible associations with heliogeophysical activity (HGA) components exhibiting similar cyclicity. Methods: Annual incidences of SMM from 5 countries (Czech Republic, UK, Bulgaria, USA and Canada) over various time spans during the years 1964~1992 were analyzed and their correlations with cyclic Rz (sunspot number) and aa (planetary geomagnetic activity) indices were summarized. Periodogram regression analysis with trigonometric approximation and phase-correlation analysis were applied. Results: Previous findings on SMM for the Czech Republic, UK and Bulgaria have been validated, and cyclic patterns have been revealed for USA (T=8.63 years, P<0.05) and Canada (Ontario, T=9.91 years, P<0.10). Also, various 'hypercycles' were established (T=45.5, 42.0, 48.25, 34.5 and 26.5 years, respectively) describing long-term cyclic incidence patterns. The association of SMM for USA and Canada with Rz (dT=+6 and +7 years, respectively) and aa (dT=−10 and +9 years, respectively) was described. Possible interactions of cyclic non-photic influences (UV irradiation, Schumann resonance signal, low-frequency geomagnetic fluctuations) with brain waves absorbance, neuronal calcium dynamics, neuro-endocrine axis modulation, melatonin/serotonin disbalance and skin neuro-immunity impairment as likely causal pathways in melanoma appearance, were also discussed. Conclusion: The above findings on cyclicity and temporal association of SMM with cyclic environmental factors could not only allow for better forecasting models but also lead to a better understanding of melanoma aetiology.

Key words: Melanoma incidence, Cyclicity, Heliogeophysical activity (HGA), Forecasting, Skin neurobiology
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INTRODUCTION

The increase of skin malignant melanoma (SMM) has promoted the issues of its prevention and earlier diagnosis. Precise forecasting of incidence trends of this cancer and better allocation of resources are invaluable for national health systems worldwide. In our previous studies we have, for the first time, described cyclicity in temporal variations of incidence rates of SMM in East Bohemia region (Czech Republic), Northwest region of England (UK) and Bulgaria (Dimitrov, 1993a; 1993b; Dimitrov and Komitov, 1995) and suggested that it is associated with cycles in heliogeophysical activity (HGA). HGA is a natural ecological cyclic multicomponent factor consisting of interrelated physicochemical processes

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and irradiations of cosmic (spatial/solar or terrestrial) origin, with fluctuations of their amplitudes at various frequencies (from hours, days to tens of years). HGA mainly comprises of such phenomena as sunspot activity and geomagnetic fluctuations, but it may also refer to a number of other photic or non-photic events (e.g., solar UV radiation, solar wind, 10.7-cm solar radio flux, earth-ionosphere cavity/Schumann resonances, etc.) indicated by parameters or indices (sunspot index *Rz*, geomagnetic index *aa*, ozone concentration, etc.). Most of these phenomena have been known, observed and measured since antiquity and, although showing notable fluctuations, they have been relatively constant (permanently present) as events in the human environment. As of note, the 11-year sunspot cycle (*Rz* index) has been a consistent observation over hundreds of years (Dimitrov *et al*., 1998; Ettler, 1987; Guering-Galaktionova and Kupriyanov, 1971; Houghton *et al*., 1978; Komitov, 1986; Valev, 1986).

Incidence rates of SMM have increased in many countries during the study period and are subject to many variations (Dimitrov, 1993a; 1993b; Dimitrov and Komitov, 1995; Dimitrov *et al*., 1998; Ettler, 1987; Guering-Galaktionova and Kupriyanov, 1971; Houghton *et al*., 1978). Usually, forecasting of incidence trends relies on linear regression model over time but such simple extrapolation has very often shown big discrepancies between estimates and real values. Therefore, other approaches in forecasting are needed, at least the following: (1) non-linear regression model over time; (2) linear and non-linear regression models to independent variables with deterministic temporal patterns (seasonality, cyclicity, etc.). Currently the relationship of heliogeophysical cycles to disease dynamics is of increasing importance in view of the new 11-year solar cycle No. 24 that has just started on Jan. 4th, 2008 (http://www.physorg.com/news119271347.html).

The aim of this contribution was: (1) to restate cyclicity as a deterministic pattern of incidence variations for malignant melanoma in different countries, (2) to consider infra-annual cycles in short-term forecasting of incidence trends, (3) to assess statistical associations of incidence rates of SMM with HGA, (4) to compare temporal patterns of SMM across different countries, and (5) to suggest likely applications of such temporal relationships.

MATERIALS AND METHODS

Incidence rates of SMM (ICD9, Dx:172) during different time periods for Bulgaria, East Bohemia region (Czech Republic), Northwest region of England (UK), Ontario (Canada) and USA have been discussed in this contribution (Table 1). It should be noted that data on crude annual incidence rates of SMM for East Bohemia (excluding the districts of Pardubice and Svitavy) and on the global solar radiation (GSR) index were obtained from the original paper in Czech Republic (Ettler, 1987). Datasets consist of crude or standardized incidence rates per 100000 persons for each calendar year (Dimitrov, 1993a; 1993b; Dimitrov and Komitov, 1995; Dimitrov *et al*., 1998). The solar activity index (*Rz*) and the planetary geomagnetic index (*aa*) were used as independent variables. Heliogeophysical indices may be found in the Prompt Reports of NOAA, USA in 1992 and currently also are online (e.g., http://www.ngdc.noaa.gov/stp/SOLAR/ftpsunspotnumber.html), even on a monthly/daily basis (http://www.dxlc.com/solar/). All original data is public and/or is available from the authors upon written request.

Different statistical methods for time-series analyses and models were used as follows: descriptive statistics, linear and non-linear regression models over time, periodogram regression analysis (PRA) with trigonometric approximations (TA), linear phase-correlation analysis (PCA) and statistical tests with 95% confidence limits (Dimitrov, 1993a; 1993b; Dimitrov and Komitov, 1995; Komitov, 1986; Valev, 1986). PRA was previously described elsewhere (Dimitrov, 1993a; 1993b; Komitov, 1986; Valev, 1986). The regression equation of periodic mode for the derivation of cosine-sine estimates of incidence rates is presented below:

$$F(t) = a_0 + \sum_{i=1}^{2}\left(A_i \cos\frac{2\pi t}{T_i} + B_i \sin\frac{2\pi t}{T_i}\right), \quad (1)$$

where a_0 is the mean of the frequency $f(n)$ in the sample, *A* and *B* are coefficients of the regression line, *T* is the length of a 95% statistically significant period, *t* is the current moment of time (a serial number of the year: 0, 1, 2, 3, ..., $n-1$), and *n* is the total number of values in the series of data. PRA, whether using basic, detrended or decycled time series, also allows a description of 'hypercycles' (defined as such because the length of their period exceeds the length of data series (Dimitrov *et al*., 1998)); these hypercycles may also be included in TA model when able to improve the forecasting power, as appropriate. The TA (cosine-sine) approach relies on a prognostic index (PI), whereas PI should be above 0.25~0.3 to allow 25% of data series length forecasting ahead (Ettler, 1987; Komitov, 1986).

RESULTS

All results are summarized in Tables 1 and 2. The best regression models over time for all datasets have been shown to be non-linear: $y=a\times\exp(b/t)$ for Bulgaria, $y=a+b\times t^2$ for East Bohemia and Ontario, $y=a+b/t^2$ for USA, etc. This has indicated that forecasting of the rates only through linear models will be unreliable.

Our previous time-series analyses have revealed different cycles in incidence rates for SMM in Bulgaria (period T=12.2 years), East Bohemia (T=7.5~7.63 years), Northwest region of England (T=11 years) and USA (white females, T=8.75 years) (Dimitrov, 1993a; 1993b; Dimitrov and Komitov, 1995). The present results have revealed also cycles in the incidence of SMM for Ontario (T=9.91 years) and USA total population (T=8.63 years, short arrow in Fig.1). Hypercycles were also revealed. The long arrows on Fig.1 show the hypercycles for Bulgaria (T_H=48.25 years) and USA (T_H=34.5 years).

Table 1 Cyclic patterns of variations in annual incidence rates of SMM across different countries

Country	Pattern	Period T (year)	R	P_R	n (year)	Time interval
Bulgaria#	Cycle	12.20	0.35	<0.050	24	1969~1992
	Hypercycle	48.25	0.91	<0.001	24	1969~1992
East Bohemia (Czech Republic)#	Cycle	7.50~7.63	0.42	<0.050	22	1964~1985
	Hypercycle	45.50	0.89	<0.001	22	1964~1985
Northwest region of England (UK)#	Cycle	11.00	0.45	<0.050	20	1974~1993
	Hypercycle	42.00	0.90	<0.001	20	1974~1993
Ontario (Canada)	Cycle	9.91	0.33	<0.100	20	1964~1983
	Hypercycle	26.50	0.96	<0.001	20	1964~1983
USA	Cycle	8.63	0.40	<0.050	17	1973~1989
	Hypercycle	34.50	0.97	<0.001	17	1973~1989

R: Correlation coefficient from the periodogram (i.e., periodogram regression analysis) indicating a peak at particular period T of an underlying cyclic pattern (for example, see peridograms on Fig.1); P_R: Statistical significance of R after the z-test at $P<0.05$ when $R>1.96\times S_R$ ($z=R/S_R$), where S_R is the standard error of R; n: Sample size of time series in years. #See text for earlier references by Dimitrov (1993a; 1993b) and Dimitrov and Komitov (1995)

Table 2 Associations of indices of heliogeophysical activity (HGA) with incidence rates for SMM across different countries

Country	HGA index	Lag-period dT (year)	r	P_r	df
Bulgaria#	*Rz*	+2	+0.47	<0.020	20
	Rz	+12	+0.72	<0.001	10
East Bohemia (Czech Republic)#	*GSR*	+6	+0.49	<0.050	14
	Rz	+12	+0.52	<0.050	8
Northwest region of England (UK)#	*Rz*	+4	+0.43	<0.050	14
	Rz	+10	−0.51	<0.050	8
	aa	+8	+0.30	<0.100	10
	aa	+11	−0.63	<0.001	7
Ontario (Canada)	*Rz*	+7	+0.57	<0.050	11
	aa	+9	+0.70	<0.010	9
USA	*Rz*	+6	−0.51	<0.050	9
	Rz	+13	+0.98	<0.050	9
	aa	−10	−0.89	<0.010	5

Rz: Sunspot index; *aa*: Planetary geomagnetic index; *GSR*: Global solar radiation index; r: Correlation coefficient; P_r: Statistical significance of r; *df*: Degrees of freedom. #See text for the earlier references by Dimitrov (1993a; 1993b) and Dimitrov and Komitov (1995). For the time intervals in each country, see Table 1

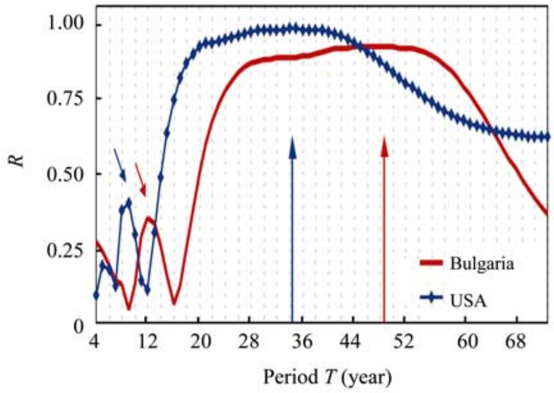

Fig.1 Cyclic patterns of variations in incidence rates for skin malignant melanoma in Bulgaria (1969~1992) and USA (1973~1989)

The curves present the spectrum R, illustrating infra-annual cycles for Bulgaria and USA. The peaks on the periodograms indicate the significant periods as denoted by vertical arrows: Short arrows (cycles with period): $T_{Bulgaria}$=12.2 years, T_{USA}=8.63 years; Long arrows (hypercycles with period): $T_{H\text{-}Bulgaria}$=48.25 years, $T_{H\text{-}USA}$=34.5 years

Furthermore, both cycles in the incidence rates as above have been used in bi-cyclic cosine-sine model. Model curve estimates for Bulgaria and USA are presented in Fig.2. The index PI indicating the forecasting power of SMM models shows a higher value for USA (PI=1.50) than for Bulgaria (PI=1.02). Cyclic patterns in estimated rates of SMM up to 1995 are clearly seen (3~6 years ahead within the rectangled areas for Bulgaria and USA).

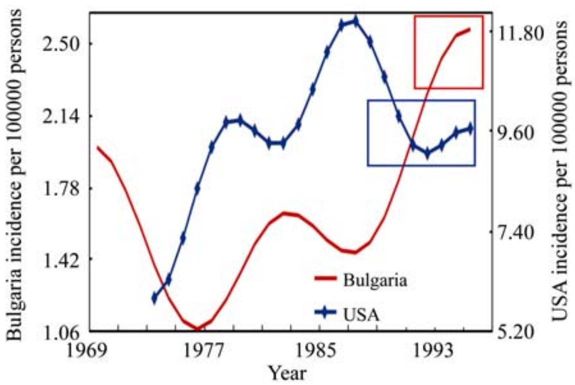

Fig.2 Model curves of variations in incidence rates for skin malignant melanoma (SMM) in Bulgaria and USA after trigonometric approximation to the significant cycles in the time series

The best fit of original data to the nonlinear models has been defined by estimates of the cyclic components in incidence variations. The curves demonstrate more clearly the peaks and falls of incidence rates over time. The rectangles indicate the model incidence estimates a few years ahead (till 1995) as an illustration of the potential for forecasting the incidence rates through extrapolation

On account of the eventually insufficient power of this cycle-based-only forecasting in particular (cyclic patterns alone by the above mentioned cosine-sine model), temporal associations of the sunspot index Rz and the planetary geomagnetic index aa, with rates for SMM, have been also analyzed. The latter approach may also give better insight into the aetiology of SMM (Table 2). The association of SMM in Bulgaria and USA with the index Rz is presented in Fig.3 as an illustration of this approach. The lag-period dT is positive when the extremes of the incidence rate follow the extremes of the sunspot index Rz. Notably, the strongest relationships are most likely to occur on the descending slopes of the 11-year sunspot cycle—positive coefficients of correlation about 2~5 years after the peak of the present solar cycle (Fig.3, left short arrow as for SMM in Bulgaria) and about 1~2 years after the peak of the next one (Fig.3, right short arrow as for SMM in both Bulgaria and USA). A negative coefficient of correlation for USA described in Fig.3 (long arrow) confirms the above findings. In conclusion, maximal

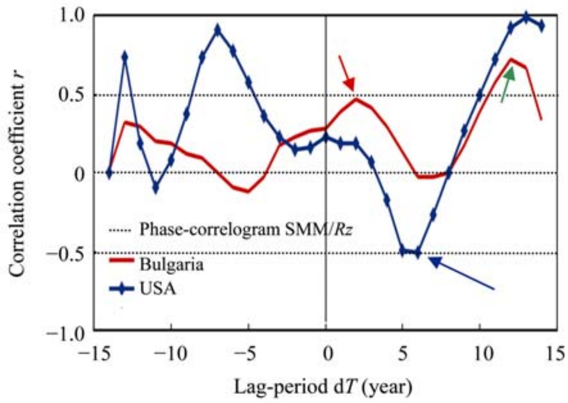

Fig.3 Phase-correlation analysis (PCA) of relations of the incidence of skin malignant melanoma (SMM) in Bulgaria and USA with the sunspot number (Rz)

Spectrum of coefficients of correlation (r) after PCA. The phase-correlogram (i.e., cross-correlogram) illustrates the temporal relationship between the time series of the sunspot number (Rz) with the time series of SMM incidence rate in Bulgaria (line, short arrows) and USA (line with rhomboids, long arrow and right short arrow). The lag-period dT is positive if it is assumed that the time series of SMM (e.g., peaks and falls) follow those of the solar sunspot index Rz whereas 3 peaks (local spectral maxima) on the phase-correlograms may be noticed. The peaks indicate the most likely lag-period with positive dT with which the relationships are expressed (Bulgaria: dT=+2 years with r=0.470 and dT=+12 years with r=0.724; USA: dT=+2 years with r=0.184, dT=+6 years with r=−0.510 and dT=+13 years with r=0.989) rates for SMM are most likely to appear out of phase, in view of the 11-year sunspot cycle. The incidence rates oscillate with a linear-phase mode to the cyclic index *Rz*, which also confirms their cyclic patterns.

DISCUSSION

Descriptive analyses have shown normal distribution of incidence rates only for SMM in Bulgaria, Czech Republic and UK (females), but the best fitting indicated nonlinearity; therefore, the best forecasting approach with time series would have required more complex, nonlinear models.

We summarized and validated the existence of cyclic patterns (cyclicity) in SMM incidence rates and/or their variations (when an existing main linear or cyclic trend is removed) across different regions and time intervals. The analyses have also confirmed the existence of 'hypercycles' as being similar to those found earlier in breast cancer incidence variations (Dimitrov *et al*., 1998). It should be noted that other authors (Houghton *et al*., 1978; Wigle, 1978) had previously presented cyclic patterns in SMM incidence rates, in Connecticut and New York (USA) and Alberta and Saskatchewan (Canada) by curves against the time of observation (8~11 year intervals between peaks), but these authors had neither analysed nor proved statistically any of the cycles they illustrated. Clearly, if proved and estimated statistically, such cyclic patterns may be successfully decomposed, reconstructed and used by trigonometric approximation and the time series could be forecasted ahead (e.g., rectangled areas in Fig.3), thus providing better estimates of future incidence rates than those produced by linear models alone.

We also established lagged temporal associations of SMM incidence rates with the sunspot index *Rz* and planetary geomagnetic index *aa*. The latter approach may also give better insight into the aetiology of SMM and the time lag between an eventual first hit (initiating event) and the later clinical appearance of cancer. Notably, the strongest relationships are most likely to appear out of phase, that is, on the descending slopes of the 11-year sunspot cycle.

Last but not least, cyclic patterns for a number of cancers other than SMM were also described in different countries (breast cancer: Bulgaria, T=17.625 years; USA, T=20.5 years) (Dimitrov *et al*., 1998). On the other hand, earlier results (Houghton *et al*., 1978; Wigle, 1978) indicated that the appearance of SMM peaked about 1~3 years after sunspot peaks. An earlier study on data from Turkmenia (former USSR) has found that maximal rates for different cancers are most likely to appear also around the minima of the sunspot cycle (Guering-Galaktionova and Kupriyanov, 1971). It should be noted that the cyclic patterns for SMM differ in the length and level of significance across different countries. However, both the usual infra-annual cycles and infra-annual hypercycles as well as some statistical associations with *Rz* (dT=+11~+13 years, on average) are similar across different countries. The recent findings, from a time-series analysis on population exposure to UV radiation over a very long time interval from 1920 to 1995 in Finland (Kojo *et al*., 2006), confirmed our results by indicating that the most likely lag-period of +5~+19 years prior to melanoma appearance might be the most relevant "silent" period in the aetiology of melanoma as related to solar UV radiation.

Temporal distributions of cancer incidence peaks along the 11-year solar activity cyclic curves (i.e., lagged correlations) may give rise to interesting conjectures. Plausible biophysical pathways for these cyclic non-photic HGA influences in the later appearance of SMM may be direct, with a predominantly local receipt of the impact by UV irradiation, solar protons or heavy-charged particles (Cucinotta and Durante, 2006; Encinas *et al*., 2008) on the epidermal, adnexal and dermal cells or cutaneous nerve endings. The direct effect may be targeted, acting upon the melanocytes and interfering with their melanocytic defence system (MDS) (Dimitrov *et al*., 2007), or it may firstly be spread, initially intermediated by the surrounding microenvironment (e.g., bystander effect, skin neuroendocrine system (Slominski, 2005) signalling, and adjacent skin neuro-immunity impairment). Alternatively, or in parallel, these pathways may be also indirect, by impacts of solar coronal-related geomagnetic storms, gravitational field changes, low-frequency (LF) geophysical fluctuations or Schumann resonance signals (Cherry, 2002; Kamide, 2003; 2005) on the brain activity, neuroendocrine axis modulations and haemato-immunological variations (Kamide, 2005). For instance, a nonlinear resonant detection/absorption of Schumann resonance signals by LF brain waves (the same frequency ranges!), through interaction with neuronal calcium ions and subsequent melatonin/serotonin balance alterations, was suggested (i.e., the reduced melatonin may cause enhanced DNA damage that can initiate, promote and progress towards cancer) (Cherry, 2002). The spectral elements in physiological chronomes (time structures) may intermodulate with physical environmental chronomes. This could lead to rhythmically recurring and predictable phase responses (i.e., feedsidewards) at population level such as cancer incidence peaks as lagged to previous peaks of the original stimuli (phase-correlation), with or without inclusion of phylogenetic and ontogenetic memories (Halberg *et al*., 2004). It is interesting that during the declining phase of the 11-year solar cycle, coronal activity is reaching a peak causing geomagnetic disturbances near the Earth orbit (for example, an intense storm can result from the superposition of two successive moderate storms driven by two successive structures in the solar wind) (Kamide, 2003). The latter effects may interfere not only with the Schumann frequencies and provoke carcinogenic stimuli (e.g., via the LF resonance with brain waives) but may also intermodulate with other cyclic cosmic influences (e.g., galactic cosmic rays, solar proton flux) that have also been related to increased cancer risk (Cucinotta and Durante, 2006) or sensitivity of quiescent neural stem cells (Encinas *et al*., 2008). These impacts and mechanisms could be linked not only to SMM appearance but together with environmental light effects and melatonin disturbances, to breast (Srinivasan *et al*., 2008) or other solid cancer occurrences as well.

Notably, such univariate (cyclicity) and bi-variate (lagged correlation) temporal relationships that we described and summarized cannot only contribute to better forecasting of the incidence trends but also foster research on the role of global and very ancient but not directly or easily treatable physical ecological factors, not only in the aetiology and development of SMM, but also in the environmental epidemiology of solid malignant tumours.

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