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RESEARCH ARTICLE

A link between cold environment and cancer

Ankit Sharma · Harphool Kumar Verma · Savitri Joshi · Mahaveer Singh Panwar · Chandi C. Mandal

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Abstract Many risk factors such as smoking and change of life style have been shown to promote genetic and adaptive epigenetic changes responsible for tumorigenesis. This study brings environmental temperature as a cancer causing factor to light. The cancer mortality rate (CMR) of a country was correlated with 17 different variables. Multivariate analysis of a total of 188 countries found that the average annual temperature (AAT) of a country might have a significant contribution to cancer death when compared with other factors such as alcohol and meat consumption. Univariate analysis found a negative correlation between AAT and CMR. All these countries were categorized into three temperature zones (zone I, −2 to 11.5 °C; number of countries, 38; zone II, 11.6 to 18.6 °C; number of countries, 32; and zone III, 18.7 to 30 °C; number of countries, 118). Out of the top-most 50 countries having the highest CMR, 26 (68.42 %), 10 (31.25 %), and 14 (11.66 %) belong to zone I, zone II, and zone III, respectively. Out of the least 50 countries having the lowest CMR, 1 (2.63 %), 4 (12.5 %), and 45 (37.5 %) belong to zone I, zone II, and zone III, respectively. CMR is low in those countries situated near to the Torrid zone (33° N to 23.5°S), but it is high for those countries situated away from these two latitudes. These data indicate that cold temperature may have a contribution in increasing tumorigenesis. High metabolic stress, which is the result of maintaining our body temperature against a cold environment, could be the possible cause for the higher cancer mortality.

Keywords Cancer mortality · Body temperature · Environmental temperature · Metabolic stress · Temperate zone · Tumorigenesis

Ankit Sharma and Harphool Kumar Verma contributed equally to this work.

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A. Sharma · H. K. Verma · C. C. Mandal (✉)
Department of Biochemistry, Central University of Rajasthan, NH-8, Bandarsindri, Kishangarh, 305817 Ajmer, Rajasthan, India
e-mail: chandicmandal@gmail.com

S. Joshi · M. S. Panwar
Department of Statistics, Central University of Rajasthan, Rajasthan, India 35817

Introduction

Cancer is not only the second most leading cause of morbidity and mortality of patients [1], but cancer mortality and its associated cost also account for a largest health economic burden worldwide. Advances in diagnosis and treatment of cancers increases overall survival time of patients; however, the rate of cancer incidence and its associated deaths are still increasing worldwide. Cancers are very complicated heterogeneous diseases. Specific types of cancer have distinct types of genetic alteration, oncogenic signaling, tumor suppressive signaling, metabolic features, and epigenetic changes which are responsible for tumorigenesis [2–6]. Moreover, molecular biology and pathophysiology of one sub-population of tumor cells differs highly from other subsets within the same tumor and tumor type. Many environmental and sociological factors including smoking, nutrition transition, change of life style, and urbanization have been proposed as cancer-causing agents [7, 8]. Similarly, biological risk factors such as age, hormonal imbalance, obesity, diabetes, and hypercholesterolemia potentiate cancer formation and tumorigenesis [9–12, 1, 13]. Recent studies documented that high-glucose, cholesterol, high-cholesterol, and high-fat could be major factors involved in rewiring of metabolic programming, which results in cancer formation [14–16]. Accumulating evidence suggests that cellular stresses such as oxidative stress and metabolic stress enhance cancer formation and tumorigenesis [17–20]. Many research studies support the idea that anti-oxidant, as well as calorie restriction, may prevent carcinogenesis [21, 22]. Current emerging data suggest a link between metabolism and cancer [23]. Excessive metabolism might generate more free radicals or reactive oxygen species that may create oncogenic mutations [23].

Body tissues or cells need to supply extra energy to fight against different adverse situations such as cold stress. In this context, this article proposes that cold temperature could be a major contributing risk factor for cancer incidence and/or deaths. This study shows that countries of hot temperature zone (33° N to 23.5°S) have low cancer mortality when compared with countries of cold temperature (away from the latitudes 33° N and 23.5°S). Herein, this study also suggests that people living in low-temperature environment may suffer from cold temperature exposure. Thus, in cold environment, cells get more metabolic stress to maintain body temperature, which may lead to the develop of cancer formation.

Materials and methods

Data collection Average annual temperature (AAT), cancer mortality rate (CMR), cancer incidence rate, meat-, alcohol-consumption, gross domestic product (GDP), body weight, physical inactivity, smoking, obesity, and CO_2 emission of a country were collected from the respective websites (Supplementary Table S1). AAT (degrees Celsius), alcohol (liters per year), wine (liters per year), spirit (liters per year), beer (liters per year), meat (kilograms per person per year), body weight (kilograms), physical inactivity (percent), smoking (percent), obesity (percent), and CO_2 (metric tons per capita) were considered for this study.

Statistical analysis R software version Rx64 3.1.1 was used for multivariate analysis. This software analysis data provide Akaike Information Criteria (AIC) [24] values which correlate the relation with the dependent variable to different independent parameters and also defines the rank of their relations to the defined variable. Kendall analysis was done using the software Analyse-It [Analyse-It for Microsoft Excel (version 2.30)] to test the null hypothesis between two independent variables. If the null hypothesis is rejected then correlation coefficient can be determined between them. Correlation coefficient (tau) lies between +1 to −1. *P* value indicates whether the difference between two variables is statistically significant or not. If $P<0.05$*, it is considered statistically significant; if $P<0.001$**, it is considered highly significant.

Geographic locations of countries by World Map Creator - The World Map Creator server was used to locate the countries in the world map (http://www.amcharts.com/visited_countries/). Top-most 50 and least 50 countries having the highest and lowest cancer mortality rate are marked using this server.

Results

Multivariate analysis for cancer mortality with other factors

There are many environmental and biological factors which may contribute to the increasing risk of cancer incidence and cancer deaths. For example, meats-, alcohol-consumption, body weight, obesity, physical inactivity, CO_2 emission (as a pollution indicator), smoking, and GDP of a country/state/place may increase directly or indirectly to the cancer risk [25–27]. First, CMR of a country was correlated with 17 different variables by multivariate analysis. This analysis included data of 17 different variables in a total of 188 countries (Supplementary Table S2). Herein, we used AIC to choose the most influencing factor among the possible factors. All the analysis was done by developing the program on the open statistical software R. From AIC, we know which factor has more information or contribution to influence a dependent variable; this will have a minimum value of AIC (Table 1). We listed the all variable factors according the AIC score after initial step (Table 1) and which had minimum AIC score in comparison to other variables which were automatically eliminated in the data processing pressure by the R software. When ranked according to ascending AIC score, the most significant contributory factors in cancer mortality are correlated with AAT (Table 1). At the end of this analysis, it was noticed that wine consumption, spirit consumption, and GDP came after AAT (Table 1). This multivariate analysis suggests that AAT might have a major contribution in cancer mortality in compared with the other variable factors.

Negative correlation between cancer mortality and temperature of a country exist

To test the dependency between CMR and AAT, we used Kendall Tau hypothesis test. Kendall Tau test is a non-parametric test in which the distribution of the pair of variable is not required. We applied the test under the null hypothesis, H_0, $\tau=0$ i.e., the two variables of interest, AAT and CMR, were independent. We calculated the Kendall Tau rank correlation coefficient to understand the behavior of relationship between AAT and CMR. In this study, we used a paired data set of AAT and CMR of 188 countries. This analysis found a negative correlation between CMR within the AAT range −2 °C to 30 °C of total 188 countries ($R=-3.02$, $p<0.0001$, $Z=-6.17$, Cl=−0.395 to −0.210). Next, we measured the correlation coefficient between these two variables from the AAT range −2 °C to every 2 °C difference (Table 2), where it was

Table 1 Multivariate analysis between different variables and the cancer mortality rate

A			
Variables	AIC score	Rank	
AAT	−508.80	1	
GDP	−510.39	2	
Wine	−511.35	3	
Spirit	−513.91	4	
CO_2	−514.07	5	
Smoking	−514.35	6	
Weight	−514.56	7	
Beer	−515.54	8	
Obesity	−515.85	9	
Physical inactivity	−516.11	10	
Alcohol	−516.19	11	
Mutton	−516.71	12	
Meat	−516.72	13	
Poultry	−516.75	14	
Pork	−516.81	15	
Beef	−516.82	16	
B			
Variables	AIC score	*P* value	Rank
AAT	−513.32	0.001	1
Wine	−519.23	0.05	2
Spirit	−520.84	0.10	3
GDP	−521.22	0.01	4

R software was used to perform multivariate analysis on a total of 16 variables [Annual Average Temperature (AAT), meat consumption, beef consumption, pork consumption, poultry consumption, mutton consumption, alcohol consumption, beer consumption, wine consumption, spirit consumption, GDP, CO_2, smoking, body weight, obesity, and physical inactivity] with the cancer mortality rate (CMR). (A) is the initial step of R software processing. The analysis process automatically eliminated the variables which may not have significant correlation with CMR. (B) Further analysis selected AAT, Wine, Spirit and GDP. AAT was ranked first

noticed that negative correlation coefficient with a significant *p* value and |Z| value of ~3 started from 18 °C onwards, and this was maintained to keep higher at 30 °C, where |Z| value was also more than 3. These data indicated that CMR gradually decreases with the increase of AAT of countries (Tables 3, 4, and 5).

People living in cold temperature countries have high risk of cancer mortality

We wanted to categorize the countries by different temperature zones to know whether any particular temperature zone may have a higher risk of cancer mortality. We used the Kendall Tau statistical analysis to define the temperature zone. All 188 countries were divided into three temperature zones where zone I (cold countries), zone II (moderate temperature countries), and zone III (hot countries) defined the range of temperature from −2 to 11.5 °C, 11.6 to 18.6 °C, and 18.7 to 30 °C, respectively. No significant correlation between AAT and CMR was found within an individual zone (Tables 3, 4, and 5). Zone I, zone II, and zone III contain 38, 32, and 118 countries, respectively. We observed that the 50 top-most countries having the highest CMR, 26 (68.42 %), 10 (31.25 %), and 14 (11.66 %), are the number of countries which belong to zone I, zone II, and zone III, respectively (Table 6 and Fig. 1a). These data indicated that people living in cold countries may have a higher risk of cancer-related death, whereas hot temperature may not have this increase in risk. To verify these observations, we further analyzed the least 50 countries which had the relatively lowest CMR. This

Table 2 Univariate analysis between temperature and cancer mortality rate

Temperature range (°C) (AAT)	Tau value	Z value	*P* value
−2 to 4	−0.333	−0.68	0.4969
−2 to 6	0.360	1.44	0.1508
−2 to 8	0.057	0.36	0.7168
−2 to 10	−0.002	−0.02	0.9864
−2 to 11	0.002	0.01	0.9896
−2 to 12	−0.032	−0.29	0.7715
−2 to 14	−0.174	−0.1.82	0.0695
−2 to 16	−0.201	−2.26	0.0235
−2 to 18	−0.231	−2.76	0.0058
−2 to 20	−0.356	−4.69	<0.0001
−2 to 22	−0.399	−5.65	<0.0001
−2 to 24	−0.420	−6.33	<0.0001
−2 to 26	−0.340	−6.06	<0.0001
−2 to 28	−0.298	−6.02	<0.0001
−2 to 30	−0.302	−6.17	<0.0001

A total of 188 countries were included. Univariate analysis was carried out between two variables [CMR and AAT] in every 2 °C interval of AAT of the country, starting from −2 °C to 30 °C. Kendall analysis shows negative Tau (correlation coefficient) value with a *p* value of 0.0235 and a |Z| value of less than 3 (−2.26) up to 16 °C. However, the Tau value was negative with a significant *p* value and a |Z| value of more than 3 (-4.69 to −6.17) from 20 °C onwards to 30 °C

Table 3 Selection of temperature zone I (−2 °C to 11.5 °C)

Temperature (°C) range	Tau value	*Z* value	*P* value
−2 to 11.4	0.002	0.01	0.9826
−2 to 11.5	−0.011	−0.10	0.9199
−2 to 11.6	−0.032	−0.29	0.7715
−2 to 11.7	−0.032	−0.29	0.7715

Univariate analysis between two variables [AAT and CMR] was done up to 11.7 °C. No correlation was found between these two variables in this temperature zone. We considered temperature range −2 °C to 11.5 °C as zone I. Out of a total of 188 countries, 38 countries belong to this zone

Table 4 Selection of temperature zone II (11.6 °C to 18.6 °C)

Temperature (°C) range	Tau value	*Z* value	*P* value
11.6 to 18.1	−0.099	−0.75	0.4526
11.6 to 18.4	−0.123	−0.95	0.3439
11.6 to 18.6	−0.179	−1.43	0.1532
11.6 to 18.7	−0.255	−2.11	0.0351
11.6 to 18.8	−0.277	−2.33	0.0198

Univariate analysis between two variables [AAT and CMR] was done, where the temperature variation was 11.6 °C to 18.8 °C. A negative correlation was found between two these variables in this temperature zone with significant p value after 18.6 °C. Thus, we considered temperature range 11.6 °C to 18.6 °C as zone II. Out of a total of 188 countries, 32 countries belong to this zone

finding showed that 1 (2.63%), 4 (12.5%), and 45 (37.5%) are the number countries which belong to zone I, zone II, and zone III, respectively (Table 7 and Fig. 1b). These results further revealed that people who live in relatively hot countries may have a lower risk of cancer deaths while cold temperature may not have an increased risk of cancer deaths.

High cancer mortality in the countries of temperate zones than the torrid zone

We have marked the geographic location of the top most 50 (Fig. 2) and the least 50 (Fig. 3) countries having the highest and lowest cancer mortality on a world map to define a cancer-prone and low-risk zone. These data showed that the least 50 countries having the lowest CMR are geographically located mostly in between the latitude of 33° N and Tropic of Capricorn (33° N–23.5°S), whereas countries having highest cancer mortality are located away from these two latitudes towards the poles. Here, it should be noted that India is a country which has less CMR [rank, 36; AAT, 24.4; and CMR, 0.75, listed in the least 50 countries having lowest cancer mortality (Fig. 3)], whereas China is a country which has high CMR [rank, 25; AAT, 10.4; CMR, 1.4, listed in the top 50 countries having highest cancer mortality (Fig. 2)]. According to the literature, the northern region of China has a higher cancer mortality than the southern region of China [28–30], and the average temperature of the northern China is relatively less than southern China. Similarly, Kashmir (northern India) has a higher cancer mortality rate and lower temperature as compared with the rest of India [31, 32]. Thus, we considered a safer zone which is defined between the latitudes 23.5°S and the 33° N which passes through northern India especially below Kashmir, India, and the middle of China. These data indicated that the position of the Sun and hot environment temperature may have preventive effect in cancer mortality, but countries with a cold environmental temperature may have a higher risk of cancer incidence and/or deaths. Thus, it can be concluded that people living in countries of both northern and southern temperate zones have a high risk of cancer-related deaths than that of Torrid Zone.

Discussion

This paper is directed at determining if people living in cold countries might have a higher risk of cancer incidence and/or death. Some factors like alcohol and meat consumption may also contribute in increasing cancer risk, but this study suggests that environmental temperature (outside body temperature) is a cancer-causing factor. Our analysis found the existence of a negative correlation with statistical significance between AAT of a country and CMR. Our data also demonstrated less cancer mortality of those countries which are located closer to the equator (0°) latitude. To determine whether this inverse relationship is valid for specific cancer types, we have further analyzed to all 188 countries mentioned above, as enlisted in Supplementary Table S2. Univariate analysis (Table 8 and Supplementary Table S3) shows a negative correlation with statistical significance between AAT and CMR of various specific cancer types (e.g., lungs, ovarian, bladder, skin, pancreas, colorectal, breast, and stomach cancers). However, this analysis shows a positive correlation with AAT and CMR in the cases of liver and cervical cancers (Table 8).

The results reported herein are different than that report by a group comparing cancer incidence with AAT based on geographical location which looked at AAT by continents [33]. Cancer incidences and cancer deaths in these regions are also enlisted in this article. For example, Central America, Northern America, and Southern America are three different regions of two American Continents. AAT of Central America is relatively higher when compared with the other two regions whereas Northern America has a relatively low AAT when compared with the other two regions (Northern America is far away from the equator latitude in comparison to the other regions). The number of overall cancer incidence and cancer death are both low in Central America when compared with the other two regions whereas Northern America, which has lowest AAT, showed the highest number of cancer incidence and cancer deaths (end column of Tables 8 and 9 of this article; [33]. This inverse relationship was also noticed in cases of different cancer types including lung, breast, liver, colorectal, stomach, prostate, and esophagus, except for cervical cancer

Table 5 Selection of temperature zone III (18.7 °C to 30 °C)

Temperature (°C) range	Tau value	*Z* value	*P* value
18.7 to 30	0.028	0.45	0.6555

Univariate analysis between two variables was done between 18.7 °C to 30 °C. No correlation was found between the two variables in this temperature zone which was considered as zone III. Out of a total of 188 countries, 118 countries belong to this zone

Table 6 Top 50 countries having highest cancer mortality rate are divided into different temperature zones

Temperature (°C) zone	Number of countries belong to top most 50 {x}	Number of total countries (in the respective zone) out of a total of 188 countries {y}	Percentage=(x/y) ×100
Zone I (−2 to 11.5)	26	38	68.42
Zone II (11.6 to 18.6)	10	32	31.25
Zone III (18.7 to 30)	14	118	11.66

[33]. Similarly, the middle of Africa, which has a relatively high AAT, showed low cancer incidence as well as cancer death when compared with relatively cold northern and southern African regions. The similar trend was also observed in cases of esophagus, colorectal, lungs, breast, and prostate, except for stomach, liver, and cervical cancer. Moreover, the Eastern Asia region having lowest AAT showed relatively higher cancer incidence and cancer death for all and individual cancer types when compared with South Asia, which has high temperature. This information further supports the hypothesis that cancer mortality/incidence of a country is linked with its geographical location [33]. Moreover, it was noticed in World Cancer Research Foundation International website (Supplementary Table S1) that a higher incidence of breast, ovarian, lung, pancreas, bladder, colorectal, and prostate cancers was more in relatively cold countries such as North America, Oceania, and Europe, whereas relatively hot countries such as Asia and Africa show lower incidence of these cancers. Moreover, North America, Oceania, and Europe have a higher incidence of soft tissue cancers in compared with Asia and Africa [34]. However, similar to earlier, this inverse relationship between temperature and cancer incidence was not observed in the cases of liver and stomach cancers [34]. Liver, cervical, and stomach cancers are predominately caused by infections of hepatitis virus, human papilloma virus, and *Helicobacter pylori*, and these infections are most prevalent in developing countries (such as Africa) [35–37]. This could explain why the inverse relationship was not noticed in cases of these three cancer types. We have noticed that prostate cancer incidence is relatively higher in cold countries. USA studies also support that the higher prostate cancer incidence is linked with lack of sun and cold temperature [38], but univariate analysis has failed to show inverse correlation between AAT and prostate cancer mortality rate (Table 8). In general, countries which are closer to the equator may have a lower risk of cancer incidence and/or death when compared with countries which are away from the equator zone. Thus, it can be assumed that lowest environmental temperature may hike the cancer incidence and deaths.

To strengthen our concept, we have also analyzed cancer statistical data of USA (Cancer Facts and Figures 2014, Atlanta: American Cancer Society; 2014), where state-wise cancer incidence rate was available, and here, variations of drinking habit, diet, toxin exposure, and life styles among individuals seem to be relatively small in compared with rest of the world population. Univariate analysis found that a negative correlation exists between AAT of state and cancer incidence rate in case of females (Table 9), but this analysis failed to find similar results in the case of males. In addition, univariate analysis shows an existence of significant negative relation between AAT and cancer incidence rate of breast, urinary (male), bladder (female), and non-Hodgkin lymphoma (male and female) (Table 10 and Supplementary Table S4). A negative correlation but not with statistical significance was also found in case of other cancer types such as colorectal (female), lung (female), prostate, and pancreatic cancer (female). However, a positive trend was noticed in case of colorectal (male), lung (male), and pancreatic cancers (male) (Table 10 and Supplementary Table S4). Furthermore, cancer mortality and incidence may vary among individuals of different ethnicities and races. Thus, we have analyzed the USA data for CMR with different races and ethnicities [39]. Our data show a negative correlation between temperature and cancer mortality (all site) for Alaska Native/American Indian (both male and female). Moreover, a negative tendency was observed between AAT and other ethnicity/race such as Asia Pacific (male

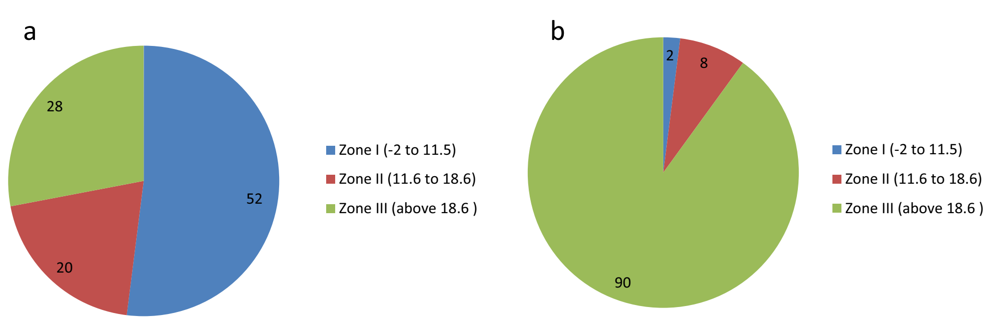
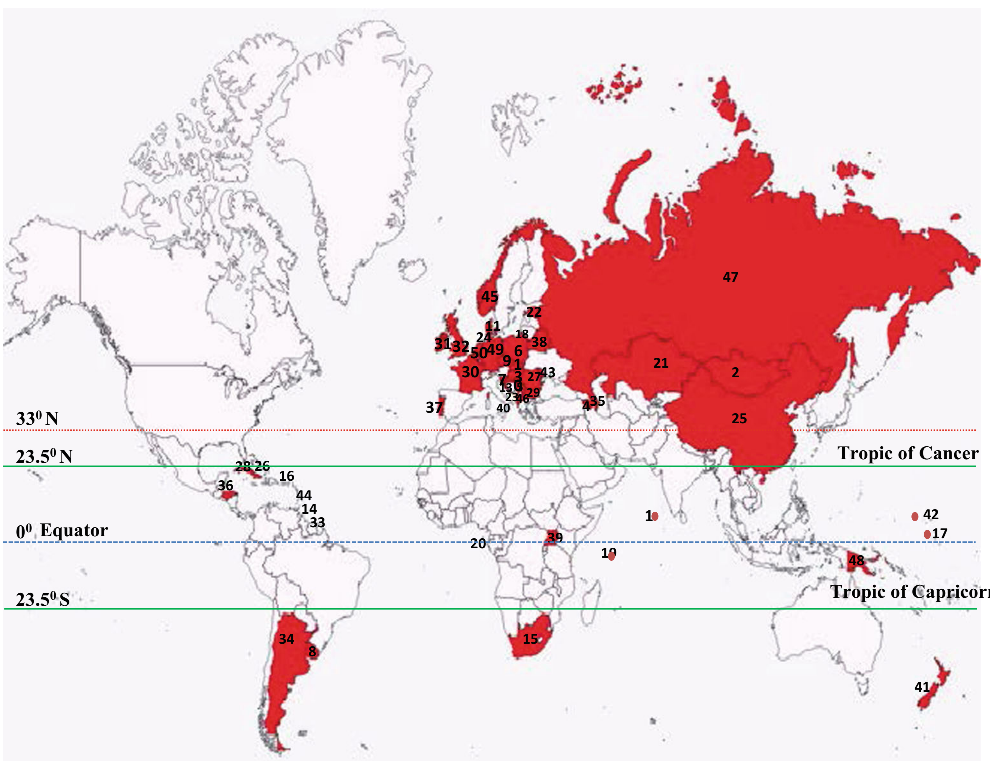


Fig. 1 Charts show the percentage of countries belonging to defined temperature zones. Distribution patterns of the top 50 countries having highest cancer mortality rate (**a**) and the least 50 countries having lowest cancer mortality rate (**b**), respectively, are shown here

Table 7 Least 50 countries having lowest cancer mortality rate are divided into different temperature zones

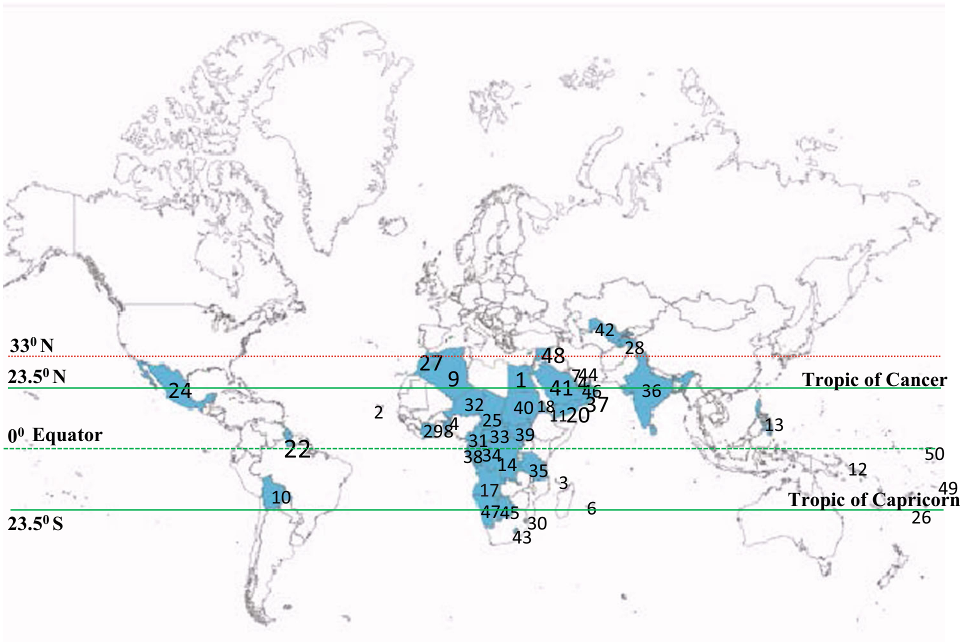
Temperature (°C) zone	Number of countries belong to top least 50 {x}	Number of total countries (in the respective zone) out of a total of 188 countries {y}	Percentage=(x/y) ×100
Zone I (−2 to 11.5)	1	38	2.63
Zone II (11.6 to 18.6)	4	32	12.5
Zone III (above 18.7 to 30)	45	118	37.5

and female), white non-Hispanic (female), white Hispanic (female), and black (female), although such negative trend was not found in cases of male white non-Hispanic and black peoples (Supplementary Tables S5 and S6). Here, temperature variation was from −3 °C to 21.5 °C. Only three states belong to temperature zone III (above 18.6 °C). Our earlier analysis of a total of 188 countries (Table 2) showed a strong negative correlation in between AAT and cancer mortality after 20 °C and onwards. It could be one of the possible reasons why this analysis has failed to show the negative correlation between these two variables in the case of males (all site) or in some other male specific cancers. In addition, migration rate from one state to other state is very high in the USA. Moreover, the number of males immigrating to the USA was higher than females up to 1970 (Supplementary Table S1). There could be many other factors which deviate the results in the case of



Rank	Country	Temp	CMR
1	Maldives	27.8	2.615
2	Mongolia	-0.5	2.06
3	Hungary	10.2	1.895
4	Armenia	7.3	1.734
5	Serbia	10.3	1.712
6	Poland	7	1.693
7	Croatia	12.7	1.655
8	Uruguay	16.8	1.641
9	C.Republic	6.7	1.581
10	Slovakia	5.7	1.58
11	Denmark	7.7	1.577
12	Latvia	5.8	1.562
13	Slovenia	8.5	1.558
14	Grenada	25	1.555
15	SA	16.4	1.554
16	Dominica	25	1.554
17	Nauru	27.2	1.543
18	Lithuania	6.3	1.531
19	Seychelles	26.4	1.524
20	STP	25.3	1.516
21	Kazakhstan	5.7	1.509
22	Estonia	5.4	1.493
23	Albania	13.7	1.478
24	Netherlands	9.6	1.471
25	China	10.6	1.451
26	SKN	26.4	1.443
27	Romania	8.8	1.433
28	Cuba	25.3	1.416
29	Bulgaria	8.7	1.389
30	France	10.7	1.384
31	Ireland	9.2	1.374
32	UK	9.8	1.37
33	Barbados	26.1	1.358
34	Argentina	15.1	1.353
35	Azerbaijan	13.1	1.347
36	Honduras	25.4	1.347
37	Portugal	15.2	1.343
38	Belarus	7	1.338
39	Uganda	21.1	1.328
40	Lebanon	15.9	1.32
41	NZL	12.3	1.316
42	Tuvalu	27.2	1.314
43	Molodova	9.7	1.308
44	A &B	27.2	1.307
45	Norway	4.4	1.303
46	Macedonia	11.5	1.299
47	Russia	5	1.298
48	PNG	24.9	1.281
49	Germany	8.1	1.275
50	Belgium	9.3	1.275

Fig. 2 Geographical distribution of the top-most 50 countries having highest cancer mortality rate (CMR). *Red color* marked countries are the top-most 50 countries with highest CMR. CMR, temperature, and rank of the countries are shown in the *right panel*. Here, Tropic of Cancer (23.5° N), Tropic of Capricorn (23.5°S), 0° latitude are shown on the world map. SA: South Africa, STP: Sao Tome and Principe, SKN: Saint Kitts and Nevis, A & B: Antigua and Barbuda, NZL: New Zealand, PNG: Papua New Guinea



Rank	Country	Temp	CMR
1	Egypt	21.8	0.905
2	C. Verde	23.2	0.892
3	Comoros	25	0.891
4	Qatar	26.7	0.885
5	Benin	26.3	0.879
6	Mauritius	24.1	0.875
7	Bahrain	25.8	0.874
8	Togo	26.6	0.873
9	Algeria	18.8	0.871
10	Djibouti	29.4	0.861
11	Bolivia	20.9	0.861
12	Solomon I	26.3	0.858
13	Philippines	26.6	0.857
14	DR Congo	22.9	0.856
15	FSM	27.2	0.844
16	Sri Lanka	25.6	0.843
17	Angola	21	0.842
18	Eritrea	24.1	0.833
19	Cyprus	18.7	0.83
20	Yemen	27.1	0.827
21	Tonga	24.9	0.82
22	Guyana	25.9	0.818
23	E. Guyana	25.2	0.818
24	Chad	27.3	0.815
25	Mexico	20.6	0.815
26	Niue	24.4	0.813
27	Morocco	18	0.812
28	Tajikistan	10.7	0.81
29	C D'ivoire	26.2	0.792
30	Swaziland	19.1	0.791
31	Cameroon	23.4	0.79
32	Niger	28.3	0.783
33	CAR	24.6	0.783
34	R. Congo	24.1	0.783
35	Tanzania	22.7	0.754
36	India	24.4	0.75
37	Oman	26.6	0.747
38	Gabon	24.5	0.744
39	Sudan	27.3	0.725
40	S. Sudan	27	0.725
41	S. Arabia	24.4	0.71
42	UBN	13.1	0.699
43	Lesotho	12.8	0.672
44	Kuwait	24.7	0.627
45	Botswana	20.7	0.593
46	UAE	26.8	0.592
47	Namibia	18.7	0.555
48	Syria	17.7	0.553
49	Samoa	26.1	0.537
50	Kiribati	27.2	0.535

Fig. 3 Geographical distribution of the least 50 countries having lowest cancer mortality rate (CMR). The *blue color* marks countries that are the least 50 countries with lowest CMR. CMR, temperature, and rank of these countries are shown in the *right panel*. Here, Tropic of Cancer (23.5° N), Tropic of Capricorn (23.5°S), Equator (0°) latitude are shown on the world map. Solomon I: Solomon Islands, FSM: Federal state of Micronesia, E. Guinea: Equatorial Guinea, CAR: Central African Republic, UBN: Uzbekistan

Table 8 Univariate analysis between temperature and cancer mortality rate of specific cancer types of a total of 188 countries

Cancer types	Tau value	*Z* value	*P* value
AAT vs. lung cancer	−0.418	−8.45	<0.001
AAT vs. bladder cancer	−0.276	−5.54	<0.0001
AAT vs. ovarian cancer	−0.236	−4.71	<0.0001
AAT vs. skin cancer	−0.169	−3.36	0.0008
AAT vs. stomach cancer	−0.174	−3.51	0.0004
AAT vs. breast cancer	−0.104	−2.09	0.0365
AAT vs. prostate cancer	0.044	0.90	0.3694
AAT vs. liver cancer	0.260	5.25	<0.0001
AAT vs. cervical cancer	0.306	6.17	<0.0001

Univariate analysis data of Supplementary Table S3

males (all) and in some other specific cancers, in the USA. For examples, rate of tobacco consumption is more in case of males in compared with females in the USA; smoking is an important cause of lung cancer [40]. To prove this concept, we have selected Texas and Florida states of USA to further reduce the variations in drinking habit, diet, socio-culture, and lifestyle among peoples among different counties of these states. Univariate data further show an existence of negative correlation between AAT and cancer incidence in cases of different counties of Texas (Tau value=−0.196, Z=-4.57, p<.0.0001) (AAT range from 10.9 °C to 23.6 °C) and Florida (Tau value=−0.112, Z=−1.34, p=0.1813) (AAT range from 18.7 °C to 24.22 °C) (Supplementary Table S7). Moreover, this analysis also found a negative correlation between AAT and cancer incidence rate in Texas counties in case of white population (Tau=−0.197, Z=−4.59, p<0.0001). These data

Table 9 Univariate analysis between temperature and female cancer incidence rate (all anatomical sites) by state in the USA

A		
State	AAT	Cancer incidence rate
Alaska	−3	430.3
North Dakota	4.7	410.2
Maine	5	460.6
Wyoming	5.6	384.2
Montana	5.9	421.9
Vermont	6.1	453.8
Wisconsin	6.2	419.2
New Hampshire	6.6	452.1
Michigan	6.9	433.5
Idaho	6.9	410.1
South Dakota	7.3	395.9
Colorado	7.3	396.4
New York	7.4	449.2
Massachusetts	8.8	460.4
Iowa	8.8	437.1
Washington	9.1	437.7
Oregon	9.1	429.2
Utah	9.2	357.7
Pennsylvania	9.3	454.8
Nebraska	9.3	420.9
Connecticut	9.4	456.9
Nevada	9.9	399.2
Rhode Island	10.1	462.4
Ohio	10.4	425.4
Indiana	10.9	422
Illinois	11	440.3
West Virginia	11	434.1
New Jersey	11.5	450.6
New Mexico	11.9	362.5
Maryland	12.3	415
Kansas	12.4	422
Missouri	12.5	423.3
Virginia	12.8	397.4
Delaware	12.9	443.3
Kentucky	13.1	462.4
Tennessee	14.2	416
North Carolina	15	416
California	15.2	397.1
Oklahoma	15.3	422
Arizona	15.7	371.2
Arkansas	15.8	388.1
South Carolina	16.9	401.1
Alabama	17.1	395.2
Mississippi	17.4	396.9
Georgia	17.5	403.1
Texas	18.2	389.9
Louisiana	19.1	413.6

Table 9 (continued)

Hawaii	21.1	393.4	
Florida	21.5	399.9	
B			
Temperature range (°C)	Tau value	*Z* value	*P* value
−5 to 10	0.018	0.11	0.9100
−5 to 12	0.050	0.38	0.7072
−5 to 14	0.042	0.36	0.7223
−5 to 16	−0.126	−1.16	0.2470
−5 to 18	−0.204	−1.97	0.0491
−5 to 20	−0.231	−2.28	0.0229
−5 to 22	−0.259	−2.61	0.0090
C			
Temperature zone (°C)		Number of US states	
Zone 1 (−5 to 11.5)		28	
Zone 2 (11.6 to 18.6)		18	
Zone 3 (18.7 and above)		3	

(A) Represents cancer incidence rate (all sites) and annual average temperature (AAT) (www.currentresults.com/weather/US/average-annual-state-tempratures.php) of respective US states; (B) univariate analysis data of (A). (C) Number of states belongs to different temperatures zones. Minnesota is not included here because of unavailability. Data source: American Cancer Society. Cancer Facts and Figures 2014. Atlanta: American Cancer Society; 2014

suggest that a strong negative correlation between AAT and cancer mortality/incidence may exist only when the variation of AAT is very larger among individual places/states/countries. Another study was done to prove this hypothesis where the Indian states which have highest AAT (above 25 °C) (Supplementary Table S1) show low cancer mortality

Table 10 Univariate analysis between temperature and cancer incidence rate (all anatomical sites) and specific cancers of female and male of different states in USA

Gender	Name of cancer types	Tau value	Z value	p-value
Female	Temp vs. All site	−0.259	−2.61	0.0090
	Temp vs. Bladder	−0.421	−4.22	<0.0001
	Temp vs. Non-Hodgkin Lymphoma	−0.360	−3.61	0.0003
	Temp vs. Breast	−0.261	−2.63	0.0085
	Temp vs. Pancreas (death)	−0.058	−0.49	0.6228
	Temp vs. Colorectal	−0.053	−0.53	0.5928
	Temp vs. Lung	−0.031	−0.31	0.7563
Male	Temp vs. All site	0.090	0.91	0.3653
	Temp vs. Urinary	−0.370	−3.73	0.0002
	Temp vs. Non-Hodgkin Lymphoma	−0.244	−2.46	0.0140
	Temp vs. Prostate	−0.032	−0.33	0.7432
	Temp vs. Pancreas (death)	.042	.36	.7206
	Temp vs. Colorectal	0.162	1.64	0.1013
	Temp vs. Lung	0.293	2.97	0.0030

Univariate analysis data of Supplementary Table S4. Data source: American Cancer Society. Cancer Facts & Figures 2014. Atlanta: American Cancer Society; 2014 rate as compared with relatively cold states [41]. Moreover, Rajasthan, Uttar Pradesh, and Northeast India are located in the same latitude, but Northeast India, which has relatively cold AAT, has a higher cancer mortality when compared with Rajasthan and Uttar Pradesh which have relatively higher AAT [41]. These data further support the concept that an inverse correlation between cancer mortality and environmental temperature exists irrespective of latitude location. Even so, many factors such as family history, genetic defect, urbanization, life style, medicine use, medical facility, and some other local factors might also have an influence on cancer incidence and/death. But this preliminary study has not considered these factors because of complexity.

In general, the amount of UV-B exposure is more towards the equatorial zone, and it gradually decreases with increasing of latitude. Several investigators reported earlier that sunlight exposure, especially UV-B, reduced the cancer incidence and/or deaths. It was previously hypothesized that weaker UV-B exposure at higher latitudes may account for enhancement of cancer deaths [42]. It was predicted that UV-B exposure to human skin synthesizes vitamin D which might have cancer preventive effect [42, 43]. Thus, the simple assumption was made that cancer death in the equatorial zone is decreased due to higher exposure of UV-B with the resultant vitamin D production. Until now, the only factor which has been proposed to explain the results of these ecological studies is vitamin D. Substantial data from clinical sample analysis showed a very controversial relationship between vitamin D level in serum and cancer incidence and/or deaths. For example, meta-analysis data showed very ambiguous results between vitamin D and cancer incidence while case–control studies supported the garland hypothesis (cancer mortality is highest in places where the sunlight UV-B is exposed to least amount, and the lower cancer mortality is because of lack of vitamin D synthesis in human skin [44, 42]) in the case of breast cancer [45]. A cohort study in Italy reported that there was modest protective effect of vitamin D on the risk of developing esophageal cancers, but it was somewhat less clear in case of other cancers [46]. In a study from China, it was shown that increased serum vitamin D level was positively associated with squamous dysplasia, a precursor lesion for esophageal squamous cell carcinoma, in both men and women [47]. Moreover, a prospective study was conducted in the USA to establish a relationship between serum vitamin D and cancer mortality [48]. Total cancer mortality was completely unrelated to the baseline of serum vitamin D in the whole population (men, women, Hispanic, non-Hispanic, or Mexican). They did not find any interaction between vitamin D and season [48]. Moreover, the association between vitamin D and cancer incidence has been thoroughly reviewed [49]. This article suggested a strong inverse association between vitamin D level in serum and colorectal cancer, but this relationship does not hold well in the case of prostate cancer [49]. Overall data for breast cancer are relatively sparse and inconclusive [49]. Moreover, overall cancer incidence for non-Hispanic white female is relatively higher than Black, Asian American, and American Indian females in the USA. It is also higher in cases of non-Hispanic white males in compared with male populations of Asian American and American Indian. Black males have a relatively higher cancer incidence than non-Hispanic white males in USA [50]. Moreover, breast cancer incidence is higher in case of non-Hispanic white than African American in USA (Supplementary Table S1). These data further point that cancer incidence may not be dependent only on UV exposure and vitamin D, since white people are able to make more vitamin D synthesis using equal exposure of UV light in compared with Black, American Indian, and Asian American people. Beside these, substantial data from animal and epidemiological studies suggested that UV radiation in sun light, especially excessive sunbathing and use of tanning beds, may increase the risk of skin cancer [51, 52]. Our univariate analysis of a total of 188 countries also shows an inverse relationship between AAT and skin cancer mortality, similar to other cancer types (Table 8). These observations suggest that vitamin D and UV-B may not be the sole factors accounting for the prevention of cancer mortality as it relates to geographical latitude. Thus, we should consider new environment factor(s) which may be responsible for cancer mortality and/or incidence. Recent finding suggests a link between metabolism and cancer [23]. Accumulating evidence demonstrate that enhanced metabolic stress or excessive calorie intake may enhance the cancer progression and development, whereas calorie restriction may prevent cancer [53, 54, 21, 55, 56, 23].

Very low environmental temperature (compared with our normal body temperature) may increase the cancer risk. Cells in our tissues increase metabolism to generate energy and/or heat to control normal body temperature [23]. Thus, cells of our body need to supply more energy by increasing metabolism when the outside temperature of our body is very low. It has been suggested that metabolism generates oxygen free radicals which may create oncogenic mutations [23]. It has been reported that research laboratory mice maintained at room temperature (20–26 °C) showed a higher rate of tumor formation and metastasis when compared with mice maintained at thermoneutral ambient temperature (30–31 °C) [57]. As a mechanism, they had identified a decrease of CD8+ T lymphocytes due to cold stress, which could be the possible reason for the increased tumorigenesis in the cold environment. Moreover, earlier findings showed that cancer patients are diagnosed more in winter than in summer and also that cancer patients diagnosed in the winter had a poorer survival than that of summer diagnosed patients [58, 59]. Moreover, low temperature exposure increases the lung cancer proliferation and metastasis, as demonstrated in mice model [60]. Similarly, hypothermic condition increases adipocyte-mediated cancer cell progression and metastasis. Current evidence also supports the enhancement of glioma stem cell properties in response to low temperature exposure [61]. Existence of negative correlation between thyroid cancers and environmental temperature among different states of USA has also been recently documented [62]. Moreover, prostate cancer incidence has also been linked with lack of sun and cold temperature in USA [38]. These observations further support our hypothesis, i.e., inverse relationship between outside body temperature and cancer mortality. Our findings show that the countries belonging to temperature zone I (−2 to 11.5 °C) and temperature zone II (11.6–18.6 °C) both have a higher risk of cancer incidence and/or death as compared with the countries of temperature zone III (18.7 °C and above). The countries belonging to temperature zone I have the highest risk of cancer mortality when compared with the other two zones (Tables 3, 4, and 5). These data further suggest that the increased use of air conditioning (~22 °C) in houses/cars could be a factor for increasing the cancer incidence and cancer-related death worldwide. Uses of air condition or other cooling systems are increasing rapidly worldwide including in the USA, China, and India [63, 64]. Before making a final conclusion, extensive basic and preclinical research is needed to establish the independent role of outside temperature (of the body) and use of air condition (lowering microenvironment temperature artificially) on cancer incidence and/or mortality.

Our body maintains temperature homeostasis by different mechanisms such as shivering thermogenesis, non-shivering thermogenesis, and non-exercise activity thermogenesis when we are exposed to cold environment, and eventually increase the metabolic rate to increase heat production [65]. Thus, a continuous higher metabolic activity will be there against a prolonged cold exposure. Epithelial tissues are exposed being on the outer surface of the body and cover the insides of the body cavities and organs. Basement membrane is present underneath of epithelial cells layer. Under the basement membrane, different types of tissues such as connective and adipose tissues are present. If outside temperature is decreased, receptors [such as transient receptor potential melastatin 8(TRPM8)] present in epithelial cells sense it and transmit the message via somatosensory system to hypothalamus [66, 67]. Hypothalamus will stimulate the activity of several organs such as thyroid and adrenal glands, and also muscle tissues. Usually, muscle tissues start shivering to increase body temperature when outside temperature is too low and has had prolonged exposure. Moreover, this cold exposure also activates adipose tissues, located near to the epithelial tissues to increase heat production which raises body temperature. Emerging evidence show that brown adipose tissues are also present in adult humans [68, 69]. Recent literature suggests a positive link between brown fat and cancer [70]. Brown fat is more capable to increase heat than white adipose tissue. Moreover, brown adipose tissue may supply several growth factors and cytokines which may promote carcinogenesis [68, 70]. Cancer patients contain more brown fat than control patients [70]. Cold exposure also increases the activity of brown adipose tissue [69]. Thus, it may be the case, during cold exposure, that increased metabolic activity of brown adipose tissue (more consumption of glucose) may supply many factors and fuels (such as lactate and ketones) to epithelial cells, leading to increase oxidative metabolism [71, 23, 68]. Moreover, epithelial cell itself get first shock from cold temperature, thus, it may also increase heat-shock proteins and free radical formation to maintain the metabolic activity and temperature, which may also lead to develop cancers [72, 73]. Beside these, cold sensor protein TRPM has been found to be more in various epithelial cancers such as prostate and breast cancers [74]. Cold air also stimulates TRPM in lung epithelial cells to produce many cytokines and inflammatory proteins [74]. It has also been reported that cold temperature may induce stem cell properties, cell proliferation, and decrease the CD8+ T lymphocytes to enhance tumorigenesis [57, 61, 60]. In fact, muscle cells or adipose tissues are to be affected in cold shock, but epithelial cells have more tendencies of division/proliferation. Thus, long-time cold exposure may directly or indirectly promote cell division of epithelial cells and produce anomalous signaling which may increase the chance of oncogenic mutation, and it may also lead to change the epigenetic switch, which could be the probable reasons for cold-induced epithelial carcinogenesis.

In brief, this research study suggests that cold environmental temperature can be a potential cancer-causing factor. This study concludes that people living in cold environments may have a higher risk of cancer incidence and death. Outside body temperature might have a distinct influence in altering cellular metabolism, leading to cancer. This study will definitely open a new area for cancer research.

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