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Data Availability Statement: The cancer incidence, NDVI, precipitation, temperature, solar radiation, ozone concentration, population density, and other covariates are available online: CI5PLUS: CANCER **RESEARCH ARTICLE**

Climate factors associated with cancer incidence: An ecological study covering 33 cancers from population-based registries in 37 countries

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Abstract

Cancer etiology is multifactorial, with climate change and environmental factors such as extreme weather events and ozone layer destruction potentially increasing cancer risk. Investigating climate factors with cancer incidence can provide valuable insights for prevention and future disease burden prediction. We conducted a population-based ecological study using data from the World Health Organization's Cancer Incidence in Five Continents (CI5plus, 89 cancer registries from 1998 to 2012) and the Surveillance, Epidemiology, and End Results (SEER, 607 US counties from 2000 to 2018) Program. We tracked climate factors through satellite-based remote sensing, including green space, stratospheric ozone concentration, solar radiation, precipitation, and temperature. We performed linear panel regression models to estimate the effects of both long-term exposure, lag effect, and change rate of climate factors on cancer incidences. We adjusted for smoking prevalence, air pollution, and gross domestic product (GDP) per capita to account for potential confounding factors. Our study included more than 430 million underlying populations across 37 countries. Higher green space exposure (per 0.1-unit normalized difference vegetation index, NDVI) was associated with decreased incidence of lung cancer (up to 6.66 cases [95%CI 4.38-8.93] per 100,000) and prostate cancer (up to 10.84 cases [95% CI 7.73–13.95] per 100,000). Increased solar radiation was associated with a higher incidence of melanoma, but a lower incidence of prostate cancer. No evidence was found to suggest associations between temperature or precipitation and cancer incidence. However, a rapid increase in temperature was linked to higher incidences of corpus uteri cancer and melanoma. Long-term exposure and rapid changes in climate factors may influence changes in cancer incidence, particularly lung and prostate cancers. While some associations were supported by existing evidence (such as solar radiation and melanoma), further research is necessary to investigate the etiology of novel cancer risk factors.

INCIDENCE IN FIVE CONTINENTS TIME TRENDS: https://ci5.iarc.fr/CI5plus/Pages/download.aspx; The Surveillance, Epidemiology, and End Results (SEER) Program: https://seer.cancer.gov/data/; USGS Landsat 5 TM Collection 2 Tier 1 TOA Reflectance, USGS Landsat 7 Collection 2 Tier 1 TOA Reflectance: https://www.usgs.gov/landsatmissions/landsat-data-access; ERA5-Land Daily Aggregated - ECMWF Climate Reanalysis: https:// cds.climate.copernicus.eu/cdsapp#!/search?type= dataset; TOMS and OMI Merged Ozone Data: https://developers.google.com/earth-engine/ datasets/catalog/TOMS_MERGED; GHS-POP R2023A - GHS population grid multitemporal (1975-2030): https://data.jrc.ec.europa.eu/dataset/ 2ff68a52-5b5b-4a22-8f40-c41da8332cfe; Global/ Regional estimates (V5.GL.03) of surface PM2.5: https://sites.wustl.edu/acag/datasets/surface-pm2-5/; CEIC: Global Economic Data, Indicators, Charts & Forecasts https://www.ceicdata.com/en/ products; Global Burden of Disease Study 2019 (GBD 2019) Smoking Tobacco Use Prevalence 1990-2019: https://ghdx.healthdata.org/record/ ihme-data/gbd-2019-smoking-tobacco-useprevalence-1990-2019; Code availability: https:// github.com/johnjiresearchlab/

ClimateChangeCancer.

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Introduction

Climate change can affect cancer incidence through direct and indirect pathways [1,2]. Direct pathways involve exposure to risk factors that are influenced by climate factors, such as increased exposure to ultraviolet radiation from the sun due to the depletion of the ozone layer. Indirect pathways involve changes in health's social and environmental determinants that affect cancer risk, such as disrupting access to cancer healthcare services. The Intergovernmental Panel on Climate Change (IPCC) stated in the *Sixth Assessment Report, Climate Change 2021: The Physical Science Basis*, that human influence has unequivocally warmed the atmosphere, ocean, and land. Downstream changes in the atmosphere, ocean, cryosphere, and biosphere can also impact cancer occurrence through the air, drinking water, food supply, or epidemic of infectious diseases.

The long-term influence of climate variables on cancer rates is still not well understood, especially the impact on cancer incidence, which can take years or decades to develop. Most current studies focus on the immediate effects of climate change, such as emergency hospital visits, rather than on chronic diseases like cancer [3]. These research studies have shown associations between non-optimal environmental conditions (e.g., air pollution) and cancer incidence (e.g., lung cancer) [4], the effect of climate change extends beyond direct carcinogen changes. The ecological aspects, such as green space change, global warming, ozone depletion, rain patterns, and extreme climate events, indicate a need to systematically understand the diverse impacts of climate change on human health [5,6]. Cancer development is a long and complex process, influenced by environmental factors, lifestyle choices, and genetic predispositions. Climate change's fluctuations and long-term effects, which may alter cancer rates, have become a significant area of interest. The impacts of these changes could potentially overshadow the efforts made in cancer prevention, screening, and treatment [7].

In this study, we leverage the comprehensive data in global cancer registries to explore the influence of climate factors on cancer incidence. These registries provide extensive, population-based data, enabling us to examine large-scale patterns and associations with high spatial and temporal resolution. We estimated climate-related factors with long-period accessibility in satellite-based products including temperature, precipitation, solar radiation, total column ozone concentration, and green space, defining our exposure variables as the rate of change or long-term average to capture the prevalent climate and changes over time effectively. Our analysis incorporated multiple panel models for 33 major cancer types, a selection that covers the most common and deadliest cancers globally. We looked for possible effect modification by age or gender groups. This research is a novel global analysis delving into the associations between cancer incidence, the rate of climate change, and long-term environmental exposure.

Materials and methods

Study design

We used a global ecological study design by constructing a panel dataset that compiled data on cancer incidence, demographic information, climate factors, regional economy, and population behavior, with more than 430 million underlying populations in 37 countries. The base-line climate scenario in this study is defined as the 10-year average before the first registration year of each cancer registry. We calculated the 3-year moving average of each climate factor with 0-to-10-year lags and the growth rate of climate change using the ratio of the 3-year moving average and baseline climate scenario, to assess their effect on cancer incidence.

Cancer case ascertainment

This ecological study included cancer registries from two datasets: Cancer Incidence in Five Continents, CI5plus: IARC CancerBase No. 9 publication, and the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute [Incidence—SEER Research Plus Data, 18 Registries, Nov 2020 Sub (2000–2018)]. The Cancer Incidence in Five Continents (CI5) series is a registry-based data source for the evolving trends in global cancer incidence, contributed by the International Agency for Research on Cancer (IARC) and the International Association of Cancer Registries (IACR). The CI5 databases offer in-depth data on cancer incidences as documented by community-based cancer registries, at a national or subnational level. The CI5plus provided annual incidence rates for 124 selected populations from 108 cancer registries (from 1998 to 2012), and SEER provided cancer incidences for 33 cancer types of 612 US counties, with 19 consecutive years (from 2000 to 2018). The geographical boundary of each location was extracted from The United States Census Bureau TIGER 2018 dataset and The Global Administrative Unit Layers (GAUL) 500m dataset. We excluded cancer registries that were not defined as administrative units, or not covered in the database to be matched. 33 major cancer types and one category for all cancers were included and filtered based on their ICD-10 code (Table 1).

In both registry databases, we ascertained age-standardized cancer incidences (per 100,000), by dividing the number of newly reported cancer patients each year by the total population, of each age group. The age-standardized incidence was calculated using the world standard population introduced by Segi (1960) [8].

Climate exposure assessment

We used available satellite imagery and tools for analysis from Google Earth Engine, with extraction since 1985 (S1 Table). Due to uneven distribution of climatic factors at the geographical level, we weighted the climatic factors according to the population distribution within the administrative boundaries to obtain regional exposure levels. Our analysis considered population-density-weighted greenspace, temperature, stratospheric ozone concentration, surface net solar radiation, and precipitation as climate factors. We used population density data from *Global Human Settlement Layers*, *Settlement Grid 1975-1990-2000-2014*.

To quantify residential green space, we utilized the normalized difference vegetation index (NDVI) calculated based on satellite images from Landsat-5 and Landsat-7 images from the U. S. Geological Survey. The data provides information on calibrated top-of-atmosphere (TOA) reflectance, with a resolution of 30 meters. Annual stratospheric ozone concentrations were calculated using *TOMS and OMI Merged Ozone Data produced by the Laboratory for Atmospheres at NASA's Goddard Space Flight Center*. This satellite-based observation of total column ozone concentration provides level 3 gridded data $(1.0^{\circ} \times 1.25^{\circ})$ for regional trends in ozone concentration measurements were sourced from *ERA5-Land Daily Aggregated*—*ECMWF Climate Reanalysis* [9]. The data provided aggregated values of 50 land climate variables from 1963 to the present.

Covariate

Covariates were included in the models to account for potential confounding and grouped to test for effect modification. Smoking status and particulate matter with diameter not greater than 2.5 μ m (PM2.5) were important risk factors for certain cancer types, such as lung cancer. The annual and monthly ground-level concentration of fine particulate matter (PM2.5) from 1998 to 2020 was estimated by Washington University in St. Louis estimations, by merging Aerosol Optical Depth (AOD) data retrieved from NASA MODIS, MISR, and SeaWiFS

Cancer site	ICD-10 code	Incidence, male	Incidence, female	
All cancers except non-melanoma skin cancer	C00-96/C44	309.25	244.86	
Lip and oral cavity	C00-06	1.02	0.28	
Salivary glands	C07-08	0.80	0.57	
Nasopharynx	C11	0.99	0.37	
Hypopharynx	C12-13	1.29	0.2	
Esophagus	C15	5.68	1.3	
Stomach	C16	14.65	6.6	
Colorectal	C09-10	24.89	17.92	
Liver	C22	10.84	3.38	
Gallbladder	C23	2.04	2.14	
Pancreas	C25	7.76	5.45	
Larynx	C32	4.78	0.65	
Lung, bronchus, and trachea	C33-34	43.65	21.4	
Melanoma of the skin	C43	12.74	10.42	
Mesothelioma	C45	1.17	0.28	
Kaposi sarcoma	C46	0.51	0.05	
Breast	C50		64.94	
Vulva	C51		1.06	
Vagina	C52		0.33	
Cervix uteri	C53		9.93	
Corpus uteri	C54		11.23	
Ovary	C56		8.81	
Penis	C60	0.61		
Prostate	C61	69.67		
Testis	C62	4.91		
Kidney	C64-65	10.86	5.39	
Bladder	C67	16.45	3.91	
Brain and central nervous system	C70-72	2.07	1.58	
Thyroid	C73	3.68	12.47	
Hodgkin lymphoma	C81	2.25	1.81	
Non-Hodgkin lymphoma	C82-86, C96	11.57	8.16	
Multiple myeloma	C88+C90	3.63	2.51	
Leukemia	C91-95	5.32	3.27	

Table 1. ICD-10 code of cancer types considered in the analysis and averaged incidence by gender (age-standardized rates per 100,000) during the research period.

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instruments with the GEOS-Chem chemical transport model [10]. Annual smoking prevalence by country and gender was extracted from the Global Burden of Disease (GBD) study 2019 [11].

We also included regional gross domestic product per capita as a covariate to reflect economic status, which can influence disease occurrence through improved disease screening conditions and medical care services. These data were sourced from the World Bank and CEIC: Global Economic Data, Indicators, Charts & Forecasts. In cases where data for the corresponding administrative units were missing, we utilized data from higher-level administrative units instead.

Statistical analysis

In the descriptive analysis, we calculate the recent trend of incidence of all the cancer types by annual incidence change, using a two-stage modeling framework. This approach has been

described previously [12]. In the first stage, the linear regression models for each location and cancer type were constructed to assess the relationship between the cancer incidence and year. The coefficients from these regression models represent the estimated annual change in cancer incidence for each specific cancer type in each specific geographical location. In the second stage, a univariate meta-regression model was built using the location-specific estimates from the first-stage analysis, weighted by the population [13]. The two-stage analysis is performed in regions and age groups. The models are as follows:

 $First \ stage \ model: \ N_{ij} \sim a_{ij} + b_{ij} * t$

Second stage model : $b_{ii} \sim N(m, tau^2/P_i)$

where N_{ij} is the incidence of cancer type j in location i, t is the year, a_{ij} is the intercept, b_{ij} is the coefficient, m is the overall annual change in cancer incidence, and tau^2 is the between-study variance, representing the variability in annual changes across different locations and cancer types. P_i is the average population in location i.

In the main analysis, multivariable panel linear regression models were constructed to investigate the relationships between climate factors and cancer incidence, adjusted for smoking prevalence, PM2.5 concentration, and Gross Domestic Product (GDP) per capita [14,15]. We considered the rate of climate change and long-term lagged effects, and all the outcomes (33 cancer types) in the models separately. First, we considered the 3-year moving average of each climate factor with 0-to-10-year lags in the panel regression models. In this model, the exposure period with the greatest impact on cancer incidence was identified. Next, we examined the effect of the rate of climate change (the ratio of the 3-year moving average and base-line climate scenario), adjusted for the climate factors tested in the first model. 95% Cis were then estimated for both models. The models are as follows:

1. $L_3yr_n = (Lag_{n-1} + Lag_n + Lag_{n+1})/3, n = 0, 1, ..., 10$

2. Baseline climate scenario = $\sum_{T=9}^{T} X 1_t / 10$

- 3. $X \perp cr_t = L 1_{3yr_{0,it}}$ /Baseline climate scenario
- 4. -

First main model:
$$N_{it} = \beta_0 + \beta_1 * L1_{3yr_{n,it}} + \sum_{n=0}^{10} \beta * L0_{3yr_{n,it}} + \beta_2 * GDP_{it} + \beta_3 * PM2.5_{it} + \beta_4 * Smoking_{it} + \mu_i + \epsilon_{it}, n = 0, 1, ..., 10$$

5. -

Second main model :
$$N_{it} = \beta_0 + \beta_1 * X \bot cr_{it} + \beta_2 * X \angle cr_{it} + \beta_3 * X \angle cr_{it} + \beta_4 * X \angle cr_{it} + \beta_5 * GDP_{it} + \beta_6 * PM2.5_{it} + \beta_7 * Smoking_{it} + \mu_i + \varepsilon_{it}$$

Where N_{it} is the incidence of a certain cancer type in location i and year t, $L1_{3yr,n}$ is the 3-year average of climate factor 1 with lag n year(s), L0 is the 3-year average of other climate factors, X1 the value of climate factor 1, T is the start registration year of the cancer registries, X1_cr is the change rate of the climate factors 1. The fixed effects for location i are represented by μ_i , and the error term is represented by ϵ_{it} . The models are adjusted for smoking prevalence, PM2.5, and GDP per capita. To account for multiple comparisons in the models, we performed false discovery rate (FDR) correction in R 4.2 [16] to reduce the likelihood of false-positive results in the regression outcomes.

Sensitivity analysis

Sensitivity analyses were done using different model designs, like the spatial panel regression model. We did not include this model in the main study design, because the spatial panel linear model only applied to the balanced panel data. In the spatial panel linear model, the k-nearest neighbor spatial weights matrix is generated according to the latitude and longitude of each region. The effect modifications by gender and age were tested by performing the models in different gender or age group. Moreover, the quadratic term for climate factors was added to models to test non-linear relationships and identify the optimal range.

Results

Our study included 696 regions from 37 countries, covering 430 million people in the underlying population. Table 2 provides a detailed breakdown of the locations of country-specific cancer registries, the annual tally of cancer cases, and the annually varying population size over the duration of the study. Our study locations are in North America, South America, Asia, Europe, and Oceania, with locations in the U.S. covering the largest population and number of sites. Temperature and solar radiation were negatively related to latitude, and stratospheric ozone concentration was higher in high-latitude regions. The distributions of NDVI and precipitation reflect climate zones; for example, in the Köppen climate classification system, NDVI is generally higher in zone A (tropical or equatorial zone) and zone C (warm/mild temperate zone) but lower in zone B (arid or dry zone) [17] (Fig 1).

During our study period (1998 to 2012/2000 to 2018), cancer incidence (per 100000) demonstrated diverse trends across different geographic regions (Fig 2). Notably, breast and thyroid cancers witnessed the steepest rise globally among females. The significant rise in cancer incidence within younger age groups in Asia also demands attention. In contrast, for the male demographic, data from the American registry (primarily sourced from the United States) displayed encouraging strides in curtailing prostate cancer incidence, while liver cancer incidence sustained an upward trend. More broadly, our observations indicated a greater array of cancer types demonstrating significant increases in incidence among females, highlighting that the cancer burden varies discernibly between genders.

The associations between climate factors and the risk of cancers were described (Fig 3). Elevated greenness, measured by NDVI (per 0.1-unit), is linked to decreased incidence of prostate cancer (up to 10.84 cases [95% CI 7.73–13.95] per 100,000 population), lung cancer (up to 6.66 cases [95% CI 4.38–8.93]), and colorectal cancer (up to 3.60 cases [95% CI 1.67–5.53]). Considering the lag period, the association between NDVI and cancer incidence typically reaches its peak effect size around 8–9 years prior, following a U-shaped pattern (Fig 4). Our model estimates that a 0.1-unit increase in 3-year average NDVI during a lag period of 8 years is associated with a decrease of 10.84 cases of prostate cancer per 100,000 population, accounting for 12.2% of the average annual incidence (88.6 per 100,000 population). Surface net solar radiation is positively associated with melanoma of the skin in both males (up to 3.20 cases [95% CI 1.34–5.06]) and females (up to 8.06 cases [95% CI 1.70–14.42], in population aged 45 to 59), as expected. The intensity of solar radiation occurring 6–7 years ago has the greatest impact on the incidence of melanoma in the current year, as demonstrated by different exposure windows (Fig 4).

The correlation between temperature and cancer incidence showed variation based on whether temperatures fell within optimal ranges. By incorporating a quadratic term for temperature in our model, we noted a significant correlation with prostate cancer incidence (lag = 7, coefficient of quadratic term is 0.29 [95%CI 0.10–0.48]). Within the optimal temperature ranges (annual temperatures below 19.9 degrees Celsius), warmer climates were

Table 2. Baseline characteristics of the study population.

Country	Locations (n)	Period	Average population coverage (n/year)	Average total cancer cases (n/year)	
Australia	7	1998-2012	20458788	101312	
Austria	3	1998-2012	1058615	36966	
Brazil	1	1998-2012	1193254	2510	
Bulgaria	1	1998-2012	7768022	28770	
Chile	1	1998-2012	371350	863	
China	4	1998-2012	8951762	28720	
Colombia	1	1998-2012	2041874	4074	
Costa Rica	1	1998-2012	3937504	6001	
Croatia	1	1998-2012	4403036	20829	
Czech Republic	1	1998-2012	10330106	51133	
Denmark	1	1998-2012	5432902	29291	
Ecuador	1	1998-2012	1409401	2206	
Estonia	1	1998-2012	1356986	6046	
France	10	1998-2012	7739032	38734	
Germany	2	1998-2012	2783621	16015	
Iceland	1	1998-2012	299637	1233	
India	1	1998-2012	4473938	4757	
Israel	1	1998-2012	6835882	23113	
Italy	8	1998-2012	5571039	35405	
Japan	4	1998-2012	13174317	68755	
Kuwait	1	1998-2012	978655	783	
Lithuania	1	1998-2012	3373173	14438	
Malta	1	1998-2012	401720	1519	
Netherlands	1	1998-2012	16282261	79833	
New Zealand	1	1998-2012	4109706	18894	
Norway	1	1998-2012	4669549	23312	
Philippines	1	1998-2012	5915876	7360	
Poland	1	1998-2012	1288473	4568	
Republic of Korea	5	1998-2012	18895163	55132	
Slovakia	1	1998-2012	4676249	17695	
Slovenia	1	1998-2012	2013277	9431	
Spain	8	1998-2012	6503994	30859	
Switzerland	5	1998-2012	1872646	9758	
Thailand	4	1998-2012	5352543	8431	
Turkey	2	1998-2012	5293040	10986	
U.K. of Great Britain and Northern Ireland	3	1998-2012	14495579	62805	
USA	608	2000-2018	85212605	408166	

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associated with a decline in prostate cancer incidence. In contrast, regions with higher annual temperatures (annual temperature over 19.9 degrees Celsius), which presumably experience more frequent hot days beyond the optimal temperature range, exhibited an inverse trend. Air pollution also showed a significant association with cancer incidences, a 10 μ g/m3 increment in PM2.5 was associated with the increasing incidence of lung cancer (8.07 cases [95% CI 6.49–9.65), prostate cancer (9.78 cases [95% CI 7.69–11.87]), and colorectal cancer (2.36 cases [95% CI 1.10–3.64]). Associations between precipitation or ozone levels and cancer incidence did not present strong evidence in our analysis.

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A. Distribution of average annual NDVI across cancer registries



Average annual NDVI

C. Distribution of annual average daily precipitation across cancer registries



Average precipitation/mm

E. Distribution of annual average skin temperature across cancer registries



 Average total ozone concentration/DU

B. Distribution of annual average total ozone concentration across cancer registries

D. Distribution of annual average solar radiation across cancer registries



Surface net solar radiation/10^6 Jm-2

Fig 1. Global distribution of climate variables and their changes across cancer registries (averaged for the study periods, 1998-2012/2000-2018). The climate variables were calculated by taking the annual average of daily measurements. Source of the base layer of the map: https://www.naturalearthdata.com/ downloads/10m-cultural-vectors/10m-admin-0-countries/. A. Greenness: Normalized difference vegetation index (NDVI), gridded at a resolution of 0.05°. B. Total ozone: Average of primary long-term, continuous record of satellite-based observations of total column ozone (DU). C. Precipitation: Accumulated liquid and frozen water, including rain and snow, that falls to the Earth's surface (mm). D. Surface net solar radiation: The amount of net solar radiation reaching the surface of the Earth (10^6 Jm⁻²). E. Skin temperature: Temperature of the surface of the Earth (K).

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Evidence also indicates that the rate of climate change impacts cancer incidence. For instance, the growth rate of NDVI was negatively correlated with the incidence of certain cancers, such as lung and prostate cancer, although the effect was relatively small. For each 10% faster rate of NDVI growth, compared to the baseline scenario, there would be a reduction of 1.01 cases (95% CI 0.63–1.38) of excess prostate cancer incidence per 100,000 population.

Α	1	Ameri	ica		Asia			Ocea	nia		Euro	ре
Thyroid	0.08	0.36	0.49	0.38	1.49	1.2	0.05	0.38	0.45	0.05	0.25	0.26
Stomach	0*	-0.16	-0.96	-0.07	-0.3*	-1.27	0*	-0.19	-1.11	-0.02	2 -0.48	-2.18
Prostate	-0.01	-2.37	-16.11	о	1.09	9.49	0.08	8.36	22.93	0.01	3.57	15.49
Melanoma of the Skin	-0.06	-0.13	1.28	о	-0.02*	0.15	-0.22	-0.27*	2.69	0.1	0.59	1.83
Lung and Bronchus	-0.04	-1.8	-7.89	-0.04	-0.45*	-2.41*	-0.01	-0.66	-4.89	-0.0	7 -2.03	-4.37
Liver	-0.01	0.15	1.76	-0.07	-1.05	-4.13	0*	0.78	0.75	0*	0.15	0.38*
Kidney and Renal Pelvis	0.06	0.5	0.91	0.04	0.55	0.76	0.05	0.39	0.62	0.02	0.32	0.95
Colon and Rectum	0.07	0.13*	-4.54	0.02	0.7	2.63	0.04	-0.43	-2.19	0.01	0.08*	1.2
All Sites	0.16	-4.19	-27.07	0.45	2.5	6.53*	0.07*	8.12	14.01	0.19	0.8*	13.62
Thyroid	0.36	1.33	1.2	1.44	6.79	4.67	0.2	1.15	1.07	0.21	0.72	0.82
Stomach	0.01	0.04	-0.28	-0.03*	-0.09*	-0.96	0*	-0.04*	-0.46	-0.01	-0.1	-0.83
Melanoma of the Skin	-0.05	0.23	0.73	0*	-0.01*	0.09	-0.28	-0.23*	1.59	0.16	0.67	1.19
Lung and Bronchus	-0.04	-0.74	-3.37	0.01*	0.36*	0.74*	0*	0.26	1.93	-0.01	0.82	2.73
Corpus Uteri	0.06	0.41	1.35	0.06	0.71	0.85	0.04	0.3	1.34	0.01	0.02*	0.79
Colon and Rectum	0.08	0.16	-2.88	0.02	0.45	0.91	0.06	-0.44*	-1.74	0.03	0.09*	0.59
Cervix Uteri	-0.06	-0.39	-0.65	-0.01*	-0.57*	-1.13	0*	-0.22	-0.5	-0.03	* -0.08*	-0.25
Breast	0.09	-0.98	-0.17*	0.32	3.31	3.84	0.06	-0.34*	2.02	0.14	0.7*	4.32
All Sites	0.59	0.28*	-4.52	1.92	11.23	7.02	0.18*	0.36*	3.22*	0.53	3.06	10.15
	0 to 44	45 to 59	60 to 74	0 to 44	45 to 59	60 to 74	0 to 44	45 to 59	60 to 74	0 to 4	4 45 to 59	60 to 74



Fig 2. Distribution and recent trend in cancer incidence (per 100,000) across study locations (from 1998 to 2012/ 2000 to 2018). A. Annual changes in cancer incidence (per 100,000), segregated by age groups, regions, and genders. B and C. Distribution of the annual incidence (per 100,000) of all types of cancers across the study locations. The color scheme indicates the direction of the trend: Red for an increase and blue for a decrease. Results that are not statistically significant are marked with an asterisk (*).

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Faster precipitation and temperature rise rates were slightly associated with higher cancer incidence in specific cancer types (precipitation: prostate cancer, colorectal cancer, lung cancer; temperature: melanoma, corpus uteri cancer) (Fig 5). However, we did not find a relationship between the rate of change in solar radiation and cancer incidence.

Discussion

Our study, covering more than 430 million individuals across 37 countries, has identified novel and significant correlations between climate factors and cancer incidences. We found that higher exposure to green spaces and their faster growth rate contributed to a notable decrease in lung and prostate cancer incidences in males. Solar radiation demonstrated a dual role, increasing melanoma incidence while decreasing prostate cancer incidence. Interestingly,



Fig 3. Relationships between climate factors and cancer incidence. The color of each cell represents the direction and statistical significance of the respective covariate coefficients: Red signifies positive effects, while blue indicates negative effects. The numbers shown in cells represent the coefficients of climate factors in corresponding models. NDVI: Per 0.1 unit; Precipitation: Per 0.1mm; Temperature: Per 1 K; Solar radiation: Per 10^6 Jm⁻².

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a rapid temperature rise was associated with an upsurge in melanoma and corpus uteri cancer incidences. Our results underscore the protective effect of green spaces against cancer, specifically prostate and lung cancers, illuminating the time-lagged effect of environmental greenness on cancer incidence.

Of interest in our study is the varying estimates in different exposure periods may be attributable to the period between initial exposure to climate-sensitive factors and cancer diagnosis. For instance, the NDVI lagged effect demonstrated greater significance within an 8–9 years window as opposed to more recent exposures, suggesting that prolonged exposure to high NDVI may yield more potent cancer preventive effects. An emerging number of studies detected the relationship between greenness on prostate cancer [18,19]. This protective effect may be facilitated by the enhancement of air quality, minimization of exposure to environmental pollutants, and promotion of physical activity associated with higher NDVI levels [20– 24]. Both prostate and lung cancer occurrence or prognosis may be influenced by these factors [25,26].

Furthermore, etiological evidence points to inflammation as a possible underlying mechanism. For example, increased distance-weighted vegetated land cover has been associated with improved neuroendocrine, metabolic, and immune functions, including a reduction in interleukin-8 (IL-8) levels. Lower IL-8 levels may impede cancer progression by uncoupling tumor growth from androgen hormone regulation. [27,28]. Despite these findings, the exact mechanisms and the magnitude of the NDVI effect remain uncertain. Not all studies, for instance, have consistently found an association between NDVI and lung or prostate cancer incidence, suggesting that more research is needed to understand these complex relationships fully [29].



A. Estimate of per 10^6 J*m⁻² increase of solar radiation on cancer incidence, all age, male

B. Estimate of per 0.1 unit increase of NDVI on cancer incidence, all age, male



Fig 4. Association between cancer incidence (cases per 100,000 population) and climate factors, analyzed over 10 different lag periods. Each lagged term represents a three-year sliding average. The model accounts for GDP, smoking prevalence, PM2.5 concentration, stratospheric ozone concentration, annual average temperature, precipitation, and surface net solar radiation. A. Relationship with solar radiation (per 10^6 Jm⁻²). B. Relationship with the Normalized Difference Vegetation Index (NDVI, per 0.1 unit).

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Our analysis revealed significant associations between rapid precipitation growth and the incidence of colorectal cancer, lung cancer, and prostate cancer in males, although the mechanisms behind these associations are not fully understood. One possible explanation could be





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the increased microbial contamination in public drinking water and mildew growth on food resulting from heavy precipitation events [30,31]. These conditions could induce gastrointestinal diseases [32], potentially increasing cancer risk. However, this complex pathway likely involves numerous factors and warrants further investigation. In addition to environmental

factors, dietary habits may also play a role in cancer risk. For instance, previous studies have reported an increased risk of colorectal and gastric cancer associated with a high intake of refined grains [33,34].

Our analysis detected an association between solar radiation, which is also correlated with stratospheric ozone, and skin melanoma incidence—a finding that corroborates numerous research studies. Environmental science measurements in the past four decades found UV radiation, a component of solar radiation, has increased, with ozone depletion identified as a key contributor. UV radiation is a known cancer risk factor, especially skin melanoma [35,36]. Interestingly, we found that solar radiation exhibited more immediate effects on cancer risk compared to the delayed impact of greenness on cancer incidence. This confirms that solar radiation will influence cancer risk more directly, by directly impacting genetic mutations. Notably, we also observed that higher UV radiation levels could potentially reduce the risk of certain cancers, such as prostate cancer. The double-edged sword is of interest, as the protective effect is likely due to the activation of the 1,25-dihydroxy vitamin D synthetic pathway triggered by UV radiation [37-39], through promotion of physical activity. Despite these findings, our study did not identify a relationship between the rate of solar radiation change and cancer incidence. This suggests that the relationship between solar radiation and cancer risk may adhere to a strict dose-response model, with any level of increased radiation potentially affecting health outcomes.

Non-optimal temperature, often associated with the extremes of cold and heat, is perhaps the area that has the most attention in climate change research, especially on excess mortality [40,41]. Our analysis uncovered nuanced differences in temperature-related cancer incidence associations. In areas with lower average annual temperatures, increased temperature appeared to negatively correlate with cancer incidence. Conversely, in regions with higher average annual temperatures, we observed a positive correlation. We hypothesize there is a threshold in human biological or behavioral adaptation to non-optimal temperature. Further, our findings suggest that locations with accelerated warming rates may face elevated risks for certain cancers, such as thyroid and melanoma. This could be due to heat stress-induced production of reactive oxygen species (ROS) [42], which can lead to DNA damage and consequent cancer development. Despite these findings, comprehensive population-based evidence elucidating the link between non-optimal temperature and cancer risk remains scarce.

Our research offers several strengths. First, by utilizing global time-series data, we were able to examine the long-term impact and growth rate of climate change on cancer incidence, facilitating the identification of novel associations for future exploration. Second, our analysis encompassed various climate factors and their relationship with 33 common cancers, including those overlooked in previous studies. Third, our study furnishes population-based evidence linking climate-sensitive factors with cancer risks over substantial geographic regions and extensive time scales.

Our study has several limitations that should be considered. Although we integrated a comprehensive set of adjustment variables based on prior literature, other unmeasured factors that relate to climate change or potentially influence cancer occurrence still exist, like food supply, sea-level rise, and other air pollutions (e.g., Polycyclic Aromatic Hydrocarbons, PAHs). Additionally, limited by the registry distribution, our results are mainly based on high-income or upper-middle-income countries, with only 2 low-income countries included, potentially lowering the generalizability of our findings to other regions. Despite this, our study boasts diverse and sizable population coverage from different parts of the globe, bolstering the applicability of our findings. Lastly, our study does not establish the specific pathways through which environmental factors might impact different types of cancers. For example, we do not have data to determine whether a favorable environment directly influences the development of these cancers or if it indirectly affects behaviors such as physical activity levels or smoking habits. Further research is warranted to investigate these potential mediating pathways.

Conclusion

Our study, encompassing more than 430 million individuals across 37 countries, has unveiled significant associations between climate factors and incidences of major types of cancer. We discovered novel associations. Increased exposure to green spaces was correlated with decreased incidences of lung and prostate cancers in males. Rapid increases in precipitation, for instance, were associated with higher incidences of prostate, colorectal, and lung cancers, while a temperature rise was linked to higher incidences of melanoma and corpus uteri cancers. We also confirmed the association between increased solar radiation and a higher incidence of skin melanoma, while observing a lower incidence of prostate cancer under similar conditions. These findings underscore the importance of considering the rate of change in these climate factors for future cancer and climate change research. They also highlight the significance of ongoing research into the intricate connections between climate change and cancer incidence. Such studies are essential in formulating effective strategies to tackle this multifaceted global health issue, particularly in the face of ongoing climate change. Our study adds an important perspective that adaptation to climate change can complement screening, prevention, and cancer treatment in improving overall population health.

Supporting information

S1 Table. Climate-sensitive factors considered in this analysis. (XLSX)

S2 Table. Estimate of per 0.1 unit increase of NDVI on cancer incidences in different lag periods, 95% confidence interval. (XLSX)

S3 Table. Estimate of per 10^6 J*m-2 increase of solar radiation on cancer incidences in different lag periods, 95% confidence interval.

(XLSX)

S4 Table. Estimate of per 1K increase of temperature on cancer incidences in different lag periods, 95% confidence interval. (XLSX)

S5 Table. Estimate of per 1mm increase of daily precipitation on cancer incidences in different lag periods, 95% confidence interval. (XLSX)

S6 Table. Estimate of per 10 DU increase of total ozone concentration on cancer incidences in different lag periods, 95% confidence interval. (XLSX)

S7 Table. Estimate of climate factors on cancer incidences in population aged 0 to 44, 95% confidence interval. (XLSX)

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