Title: The Negative Correlation of Spice Intake and Colorectal Cancer: A Statistical Analysis of Global Health Databases

Author names: Shinjit Mani[1*], Nathan Pramanik[1], Deeksha Rao[1], Stuti Sharma[1], Timur R. Akhmetov[2]
Degrees: [2]MD, PhD
Affiliations: [1]Medical Student, Department of General Medicine, Faculty of Foreign Students, Kazan State Medical University, Kazan, Russian Federation.
[2]Associate Professor, Department of General Pathology, Kazan State Medical University, Kazan, Russian Federation
Correspondence: *Shinjit Mani, shinjit.mani@gmail.com

About the author: Shinjit Mani is currently a fifth-year medical student at Kazan State Medical University, Kazan, Russia of a total six-year program. He completed this particular research work under the supervision of Asso. Prof. T.R. Akhmetov, at the Department of Pathology of Kazan State Medical University in 2019. Currently he is working in a preclinical laboratory-based cancer research program under the supervision of Prof. Sergei Boichuk. He was chosen for the "Board of Honor 2019" by the university for his commitment and hard work.

Acknowledgment: *We want to thank Prof. S.V. Petrov, Professor at Department of General Pathology, Kazan State Medical University, for supporting and supervising the research project.*
Financing: This Research received no financial supports.
Conflict of interest statement by authors: The authors have no conflicts of interest to disclose.
Compliance with ethical standards: This research complies with the necessary ethical standards.

Authors Contribution Statement: Conceptualization: SM, TA. Methodology: SM. Software: SM, NP, DR, SS. Validation: SM, NP, DR, SS, TA. Formal Analysis: SM, NP, DR, SS, TA. Investigation: SM, NP, DR. Resources: SM, NP, DR, SS, TA. Data Curation: SM, NP, DR. Writing – Original Draft: SM, NP, DR. Writing – Review & Editing: SM, NP, DR, SS, TA. Visualization: SM, NP. Supervision: SM, TA. Project Administration: SM, NP.

Manuscript word count: 3233
Abstract word count: 229
Number of Figures and Tables: 4 figures, 3 tables

Personal, Professional, and Institutional Social Network accounts.

- **Facebook:** https://www.facebook.com/shinjit.mani, https://www.facebook.com/nathan.pramanik, https://www.facebook.com/deeksha.rao18/, https://www.facebook.com/people/Timur-Beliavskii/100000933464636, https://www.facebook.com/Kazansmu.official/
- **Twitter:** @shinjit_mani, @FoundationSpark, @DeeRao18, -, @kazansmu

Discussion Points:

1. How does diet affect the risk of colorectal cancer in a global setting?
2. Does spice intake reduce colorectal cancer risk?

3. How much does diet and colorectal cancer risk vary between countries?

ABSTRACT.

Background: Colorectal Cancer (CRC) has multiple risk factors and depends highly on diet. Positive associations of red meat and processed meat intake and CRC have been proven, but no research has been conducted on the relation of spice intake and CRC risk. Various in-vitro studies have demonstrated the anticancer activity of chemicals present in spices, which is the main driving force for our statistical analysis.

Methods: We analyzed Global Burden of Disease (GBD) database, Food and Agricultural Organization of United Nations (FAO) database, and Global Dietary Database (GDD) using Pearson correlation statistics to find any significant correlation, mainly between spice intake and CRC risk. Data from 1990 to 2013 of 100 countries was collected for the analysis. Twenty-three-year average values (±SD) were calculated for CRC risk, spice, red meat, processed meat, vegetable, and fruit intake. CRC risk is taken as dependent variable whereas all other were independent variables. All variables were analyzed using Pearson correlation analysis. Results with $p<0.05$ were further analyzed using regression analysis.

Results: Pearson correlation showed that spice intake had a significant negative correlation ($r= -0.301$, $p=0.002$) whereas red meat ($r= 0.722$, $p<0.001$) and processed meat ($r= 0.339$, $p<0.001$) had a significant positive correlation with CRC risk.

Conclusion: Significant negative correlation between spice intake and CRC risk indicates that higher spice intake can be preventive against cancer and possibly decrease the risk of colorectal cancer in populations with higher CRC risk.

Key Words: Spices, Colorectal Cancer, Red Meat

INTRODUCTION.

Colorectal Cancer (CRC) is the second most prevalent cancer in the world both in males and females according to the Global Burden of Disease database.[1] The highest prevalence is seen among countries in Europe, North America, and West Pacific region.[1] Such global distribution is related to the fact that CRC risk is highly dependent on dietary factors. The relationship between red meat and processed meat intake and CRC has been shown multiple times in last 10 years.[2] Red meat is defined as "Meat from mammals", and processed meat is defined as "Meat preserved by smoking, curing or salting, or adding of chemical preservatives".[3] Polycyclic aromatic hydrocarbons, heterocyclic aromatic amines, and N-nitroso compounds are carcinogens found to be present in red meat and processed meat are responsible for the malignant transformation of glandular epithelial cells, which line the colon and rectum.[4] Some studies suggested positive impact of vegetable and fruit intake to deter the risk of CRC.[5] But very few studies were done so far to explore the relation of spice intake with CRC.

Spices are defined as "Aromatic vegetable substances, used to give special flavor to food".[6] Some studies have shown high spicy food intake is related to an increased CRC risk,[7-10] whereas other in-vitro studies explored the possibility of finding novel active biochemical substances with cancer preventive actions in spices.[11-24] It was found that polyphenols are abundant in spices.[11] Polyphenols are known to prevent carcinogenesis by inhibiting cytochrome P450, which prevents DNA damage by various mechanisms such as direct radical scavenging and modulation of phase II metabolizing enzymes, and can also induce mechanism of apoptosis in the event of DNA damage.[11,12] Gingerol (Ginger) and Thumoquinone (Black cumin/ *Nigella Sativa*) are other types of polyphenols that have chemoprotective actions, which are currently being explored by researchers. Thymoquinone is known to upregulate the miR-34a and downregulate Rac1 expression, decreases NF-kB and IKKα/β phosphorylation, and can decrease the activity of ERK1/2 and PI3K.[13] Gingerol, on the other hand, shows anti proliferative, cytotoxic, and antitumor activity by regulating various cellular mechanisms, such as Bax/Bcl2, TNF-α, Nrf2, p65/NF-κB, SAPK/JNK, caspases-3, caspase-9, and p53.[14,15] Turmeric is a spice extensively used in curries, which contains at least 25 active chemical substances, such as Curcumine and Turmerone, that have antioxidant, neuroprotective, cytotoxic, anti-inflammatory, antiangiogenic, antitumor activities.[16,17] Among all these, Curcumine is one of the most effective bioactive substance studied extensively so far. Curcumin can induce apoptosis in response to cell damage by various mechanisms such as downregulating COX-2, NF-kB, PI3K-AKT, and by upregulating DR5, Fas ligand, P53, P38.[18-20] It also inhibits metastasis by microRNA expression regulation, and an autophagy modulator by itself.[21,22] Other than that, coriander and cinnamon were also found to have anticancer activities.[23,24] Among the spices, Capsaicin is an exception, which is known to be tumerogenic. Capsaicin is widely found in paprika, pimento, chili, jalapenos. The carcinogenic properties are mediated through EGFR and TRPV1 pathway, to increase COX2 and induce inflammation.[25] Arguably, a low to moderate dose of capsaicin showed anticancer activity is some preclinical studies,[25,26] thus the results are conflicting.

In real world data, South Asian countries with high spice intake were seen to have lesser rates of CRC.[1] For this to be true, spice intake should have some protective effect against CRC. However, no research has been conducted on the relation of spice intake and CRC on a global scale. The contrast between research data and real-world data, and the results of previous in-vitro studies were the driving force behind this statistical analysis. Thus, we collected data from three global health databases on CRC incidence per 100,000 and five possible dietary factors, which may be responsible to modify the risk of CRC, and analyzed them to gain a global perspective of the CRC risk and its relation to diet. The aim of the analysis was to determine if there was a significant correlation between the selected dietary factors and CRC risk.

MATERIALS AND METHODS.

In total, three databases were considered for this analysis, the Global Burden of Disease (GBD) database for data on CRC,[1] Food and Agricultural Organization of United Nations (FAO) database,[27] and Global dietary database (GDD).[28] Out of 195 countries, data from 100 countries was used. We excluded the countries listed in Low Income Food Deficit Countries (LIFDC) by Food and Agricultural Organization of United Nations (N=52),[29] and also the low and lower-middle income countries as per World Bank Criteria (N=40).[30] Further, the countries with incomplete data were excluded (N=3). This resulted in 100 countries for statistical analysis, as shown in **Figure 1A**. This analysis considers populations of all ages and both males and females. A total of 95 countries (mainly LIFDC, low and lower-middle income countries) were excluded from the analysis because they had extremely low intake of the dietary factors that were selected for analysis. Including such countries with very low intake of all dietary components carries the risk of a bias in the results. Thus, the above-mentioned criteria was used to exclude LIFDC and low and lower middle income countries **(Figure 1A)**.

We included data from 1990 to 2013 for CRC incidence and all dietary factors except for the processed meat intake, for which data was only available for the years 1990, 2005, and 2010 from GDD. The five dietary factors which included were spice, red meat, processed meat, vegetable and fruit intake (**Figure 1B**). These dietary factors were chosen based on previous research.[31]

Data for all dietary factors (except processed meat) was collected from the food balance sheet of FAO database. The unit for food intake was "kilogram per annum" as shown in **Figure 1C**. Data on three categories of spices were available on FAO database i.e. 'Paprika', 'Pimento', 'Others'. Out of these 3 categories we took only the data from the category 'others'. Data for 'Paprika' and 'Pimento' was rejected as their carcinogenicity was proven previously with some conflicting results.[25] For red meat intake, we included data from categories 'Mutton & goat', 'Beef and buffalo', and 'Pigmeat'. For data of vegetable and fruit intake, we used the category 'Vegetables' and 'Fruits' from FAO food balance sheet. As an exception, data for processed meat was taken from the Global Dietary database, with the average data from the three years, 1990, 2005, and 2010, being used in the final calculation. All this data, except for processed meat intake, was further converted to average annual food intake using the formula as shown in **Figure 1C**. "Average red meat/processed meat/spice/vegetable/fruit intake" corresponds to the mean value of 24 years of data. The data on CRC was collected from the Global Burden of Disease database by the unit "Rate of incidence per 100,000" and converted to "Average annual risk (%) of CRC" using the formula as shown in **Figure 1C.** Graphical representation of the partial dataset is shown in **Figure 2.** Primary scale was used to show the "CRC incidence per 100,000" using a bar graph with corresponding standard deviation (SD) and the secondary scale is used to show the food intake "kg/annum" using line chart with corresponding SDs**.** The complete dataset is provided in **Appendix,** it contains data on Average Annual Rate of CRC Incidence per 100,000 of all 100 countries, arranged in ascending order, along with the data of all other dietary factors with SD, and 95% confidence interval (CI). This data was used for final statistical analysis. In an exception to the country "Bermuda", the data on processed meat intake was supplemented by the data of "Latin America, Central Region" from GDD in place of original data, as the original data was missing when the database was accessed. The descriptive statistics shows the mean, median, mode, SD, excess kurtosis, skewness, range, minimum, maximum, and count of all the variables (**Table 1**). The data of Average annual risk (%) of CRC is shown in **Figure 3**, as a map, where Z score of -2 to +2 was used to identify the countries according to their CRC risk. To create the map, we used the website mapchart.net, and the template of the map with microstates. Four different colour codes were used to identify the risks according to their Z-scores.

We used IBM SPSS statistics v23 for all statistical analysis. Histograms with normal distribution curves were used to visualize the data distribution of all dietary factors. Boxplots were used to compare the data distribution among the variables. Average annual risk (%) of CRC was the dependent variable and the rest were taken as independent variables. All the variables were analyzed using Pearson correlation analysis. A 95% CI of the Pearson correlation coefficient was calculated according to the formula of Fisher's transformation.[32] Scatter-dot plot was used to visualise the correlation statistics, using trend line and 95%CI of the correlation. The correlation results with $p<0.05$ were then analysed using forward and backward regression analysis for further confirmation. The data was also analysed using partial correlation analysis to determine any possible dependency between independent variables.

RESULTS.

Overall, the result shows the dynamics of CRC risk and food intake along with their correlation. **Figure 2A** describes the data on red meat and processed meat on the background of CRC incidence rate per 100,000. There was higher red meat consumption among the countries with higher CRC incidences, such as Germany (81.24 per 100000; 60.53 kg/annum), New Zealand (78.36 per 100000; 73.73 kg/annum), Denmark (72.38 per 100000; 66.88 kg/annum) with exceptions such as Croatia (65.91 per 100000; 37.16 kg/annum), and Bulgaria (51.16 per 100000; 37.86 kg/annum). Some of the countries with low CRC incidence were found to have higher red meat intake, which is similar to the countries with high CRC risk, i.e. Paraguay (6.54 per 100000; 55.21 kg/annum), Samoa (6.46 per 100000; 44.57 kg/annum), Brazil (10.76 per 100000; 46.54 kg/annum). The reverse is also observed in the case of Japan, where the red meat and processed meat intake is relatively less (28.18 kg/annum; 2.83 kg/annum) with the highest CRC incidences (82.71 per 100000) among all the 100 countries. A positive was also observed between processed meat intake and CRC incidences. However, some countries such as Panama (11.46 per 100000; 21.79 kg/annum), Colombia (9.94 per 100000; 18.55 kg/annum), and Costa Rica (14.4 per 100000; 17.93 kg/annum) had higher processed meat intake but decreased CRC risk. Overall, the trend for both red meat and processed meat consumption is positive with increasing CRC incidence. The data plot in **Figure 2B** shows most of the countries with higher CRC incidences consume low spice i.e. Germany(81.24 per 100000; 0.24 kg/annum), Italy (77.70 per 100000; 0.056 kg/annum), Czech Republic (76.8 per 100000; 0.065 kg/annum), and the opposite was seen with the countries with low CRC incidences, with some exceptions, such as Iraq (3.21 per 100000; 0.034 kg/annum), Belize (5.34 per 100000; 0.007 kg/annum), Dominican Republic (6.51 per 100000; 0.029 kg/annum) and Gabon (6.90 per 100000; 0.057 kg/annum). Altogether, there is an inverse relationship between spice consumption and CRC incidence. The data plot on vegetable and fruit intake is not shown, as the correlation was not significant.

The data on Average Annual Risk (%) of CRC in **Figure 3** clearly identified the countries of South East Asia, Middle East, North Africa and South America in a below average risk (0-0.0315%). The countries of Eastern Europe and Eurasia region have higher than average risk (0.0315-0.0569%). Most importantly, the countries of North America, Europe, and Oceania are identified with highest risk of CRC (0.0569-0.0823%). The color scheme is based on the Z-score of Average Annual Risk (%) of CRC, where blue indicates -2SD range from the mean, navy-blue indicates -1SD range from mean, brown indicates +1SD range from mean, and red indicates +2SD range from mean. The mean risk of CRC (±SD) is 0.0315 (±0.0254).

In descriptive statistics **(Table 1),** careful evaluation of Excess Kurtosis shows that the variables “Average Annual Risk (%) of CRC” (-1.11), “Average Red Meat Intake” (-1.26), and “Average Processed Meat intake” (-0.065) are platykurtic in nature with values less than 0. It is further explained using the histogram of the variable in **Figure 4A**. The other three variables are leptokurtic, with an excess kurtosis value greater than 0. Among them “Average Spice Intake” and “Average Fruit Intake” has the highest excess kurtosis of 2.73 and 4.99. These same two variables are also observed to have high skewness (positive), with skewness values of 1.8 and 1.5. The data shows that the majority of the countries have a less than average spice (mean 0.527, mode 0.472) and fruit intake (mean 101.29, mode 166.08), while a minority has a very high intake. For further understanding, we plotted a histogram chart of all five dietary factors. As shown in **Figure 4 (A-E),** the histogram shows bimodal distribution for the variable "Average Red Meat Intake", with the first one nearly at 20kg/annum and the other at 60kg/annum. This bimodal distribution is the reason of the low excess kurtosis value, as the distribution is spread widely on the tails side. Other variables had normal distributions with moderate to high positive skewness, and the mode value less than the mean values. The histogram of "Average Spice Intake" shows a very low mode value (0.472), which actually contributes to the skewness of the dataset. On the other hand, the boxplots (**Figure 4F**) provides a visual comparison between all five dietary factors. It accurately shows the range, first quartile, median, third quartile, and the outliers. The variables "Processed Meat Intake" (high 21.7, low 0.93) and "Average Spice Intake" (high 2.87 , low 0.007) have relatively small range of values, thus for proper understanding, the boxplots are shown again in **Figure 4H** and **Figure 4K**. It is important to understand that outliers that are shown in the graphs, are not excluded from the analysis, Despite being outside the range of (Q1-1.5*IQ) to (Q3+1.5*IQ) and are significant.

To determine the statistical significance, we used Pearson correlation analysis (**Table 2**). The results showed a significant positive correlation between CRC risk and red meat (r=+0.772, 2-tailed p<0.001, 95%CI .678 to .841) as well as processed meat (r=+0.332, 2-tailed p=0.001, 95%CI .145 to .496). A significant negative correlation was also found between CRC risk and spice intake (r=-0.301, 2-tailed p=0.002, 95%CI -.470 to -.111). Surprisingly, vegetable (r=0.176, 2-tailed p=0.080, 95%CI -.021 to .360) and fruit intake (r=-.035, 2-tailed p=0.733, 95%CI -.230 to .163) had no significant correlation with CRC. The scatter-dot plot for the visualization of the correlation analysis in **Figure 4G-K** shows the regression line with 95%CI which corresponds to the data given in the **Table 2.** Further investigation using linear regression analysis of the data showed the model fit or R^2 for red meat was highest (R^2=0.596) followed by processed meat (R^2=0.111) and spice intake (R^2=0.091). In forward and backward regression analysis (data not shown) we found that the predictive power of CRC risk is highest in "Average Red Meat Intake". The partial correlation (**Table 3**) was conducted to answer the question of interdependence of the dietary factors. As the results show, "Average Red Meat Intake" had a significant positive partial correlation to CRC (0.727, p<0.001), while "Average Processed Meat Intake" (-0.035, p=0.735) and "Average Spice Intake" (-0.043, p=0.675) had no significant partial correlation.

DISCUSSION.

It is worth mentioning that the negative correlation between spice intake and CRC is a novel finding. The positive correlation of red meat and processed meat with CRC is in agreement with previous studies.[4] Different research has shown conflicting results regarding vegetable consumption and fruit consumption and their effect on CRC, where some showed a negative relation, others denied any relation at all.[31,33,34] In our research, we did not find any significant correlation. Data on spice intake shows high positive skewness with mode value much less than mean value, this confirms that the majority of the countries have less than average spice intake. Model fit (R^2) plays a major role in the forward and backward regression, which explains the decreased predictive power by "Average Processed Meat Intake" and "Average Spice Intake". As per the data on partial correlation, red meat intake is found to be the major cause of CRC irrespective of the processed meat and spice intake, while processed meat intake has no significant influence on CRC by itself. And most importantly, spice intake does not influence CRC risk alone, the significant negative correlation is seen when red meat intake is considered. In conclusion, our results indicate that spice intake can have a beneficial effect among the population with high red meat intake, which may decrease the risk of CRC in the long term, but vegetable and fruit intake may not have any additional benefit to deter CRC risk. This new finding in this analysis agrees with the preclinical studies that demonstrated the anticancer properties of various spices.[5-19]

It is important to mention the limitations of this analysis. In the FAO database, there was no mention of any particular spices in the category 'others', which compromises the accuracy of the results to some extent. The other two categories 'Paprika' and 'Pimento' were not taken into the analysis. Previous studies suggested that high amounts of spicy food that are rich in chilies may cause chronic inflammation in gastrointestinal tract and in long term can trigger cancer, with some conflicting results claiming capsaicin in low doses can have anti-cancer activities.[25,26] Due to these conflicting results we did not consider 'Paprika' and 'Pimento' for the analysis. Recent data for every country was not available. Data of food intake later than the year 2013 was not available in FAO database, thus we took the data from 1990 to 2013 for our analysis. The GDD had the data only for the year 1995, 2005, 2010. These three years of data was used in calculation of processed meat intake, which may have limited the accuracy of the analysis. With more accurate data and a larger sample size the model fit of the data can be improved and enhance accuracy.

The risk of cancer can vary from population to population, depending on multiple factors from behavioral to biological. For instance, this is seen in Japan where despite high spice intake and low red meat intake, there is higher CRC risk, possibly due to their genetic predisposition for gastrointestinal cancer. This contrasts with Europe and North America, where high CRC risk is largely due to unhealthy dietary pattern containing high red meat.[35] Thus, studies conducted within a particular population may not provide an exact picture of a disease or treatment. Therefore, an analysis using global databases is important. In recent years, global health has become an important topic of discussion. It is important to view disease as a global issue which needs a large-scale solution. It is not enough to improve individual health to create a sustainable future with a healthy population. To do so requires addressing the social, behavioral and dietary changes which can be implemented on a large scale within the population. The novel finding in this analysis is the negative correlation of spice intake and CRC risk. The most important question that arises from this data is: what is the adequate amount of spice intake that can help decrease the CRC risk? Our analysis could not provide the answer yet. To answer this question, further research needs to be conducted, using different population groups with variable risks. Our results show that a simple addition of spice in the diet may be beneficial to the population where red meat intake is high, and provides an incentive to further explore the cancer preventive mechanism of the spices, and their use in the field of global health and cancer prevention.

REFERENCES.

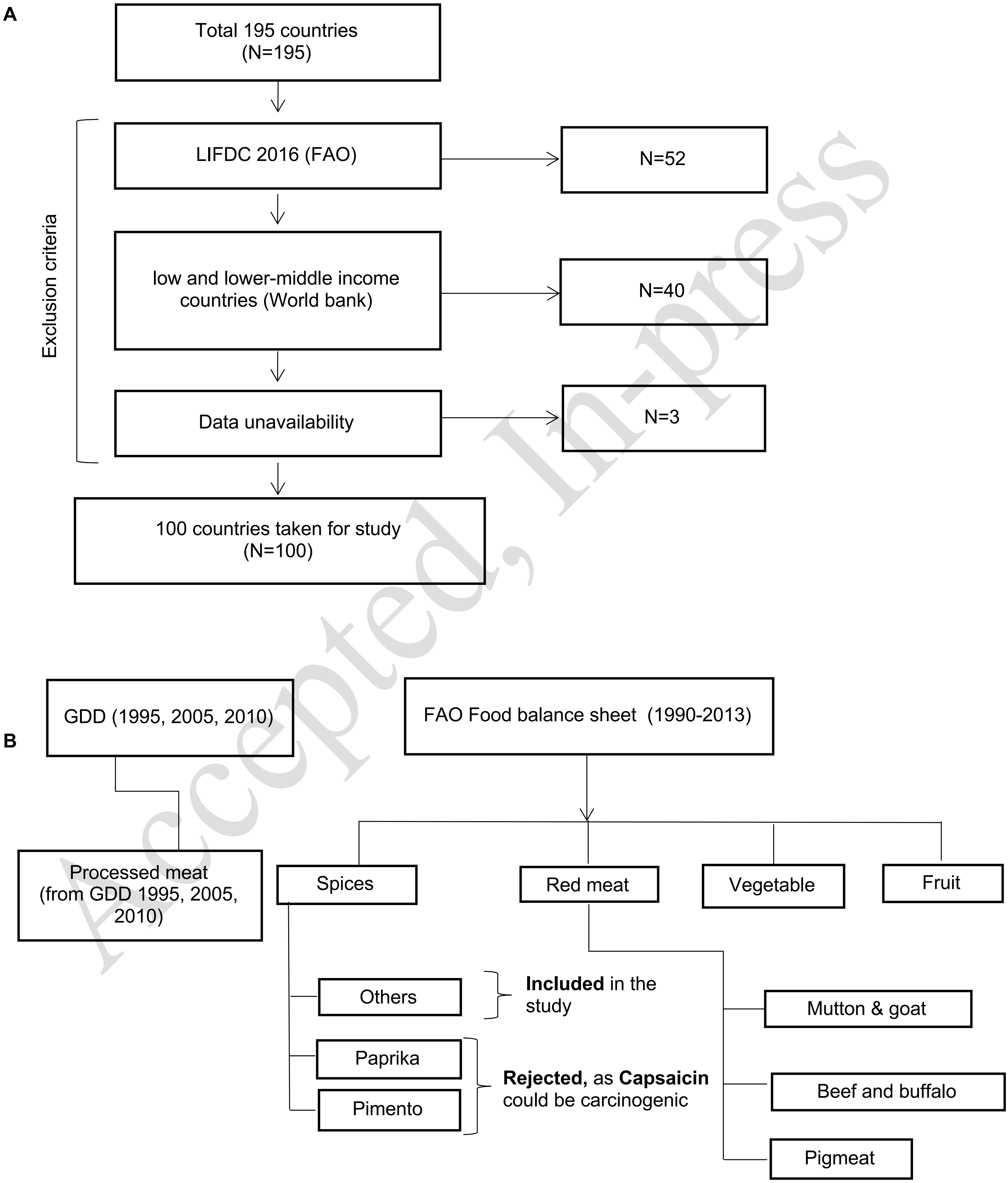
1. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2017 (GBD 2017) Results. Seattle, United States: Institute for Health Metrics and Evaluation (IHME), 2018. Available from http://ghdx.healthdata.org/gbd-results-tool; last updated Aug 01, 2020; cited Aug 01, 2020.
2. Aykan NF. Red Meat and Colorectal Cancer. Oncol Rev. 2015 Dec 28;9(1):288.
3. IARC Working Group on the Evaluation of Carcinogenic Risks to Humans. Red Meat and Processed Meat. Lyon (FR): International Agency for Research on Cancer; 2018. (IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, No. 114.) Available from: https://www.ncbi.nlm.nih.gov/books/NBK507971/; last updated March, 2018; cited Sep 17, 2020.
4. Demeyer D, Mertens B, De Smet S, Ulens M. Mechanisms Linking Colorectal Cancer to the Consumption of (Processed) Red Meat: A Review. Crit Rev Food Sci Nutr. 2016 Dec 9;56(16):2747-66.
5. Hidaka A, Harrison TA, Cao Y, Sakoda LC, Barfield R, Giannakis M, et al. Intake of dietary fruit, vegetables, and fiber and risk of colorectal cancer according to molecular subtypes: A pooled analysis of 9 studies. Cancer Res. 2020 Aug 14;canres.0168.2020.
6. Cambridge dictionary [Internet]. Cambridge University Press; c2020. Spice; [cited 2020 Sep 17]; [About-1 screen]. Available from: https://dictionary.cambridge.org/dictionary/english/spice
7. Chen YH, Zou XN, Zheng TZ, Zhou Q, Qiu H, Chen YL, et al. High Spicy Food Intake and Risk of Cancer: A Meta-analysis of Case-control Studies. Chin Med J (Engl). 2017 Sep 20;130(18):2241-2250.
8. Mathew A, Gangadharan P, Varghese C, Nair MK. Diet and stomach cancer: a case-control study in South India. Eur J Cancer Prev. 2000 Apr;9(2):89-97.
9. López-Carrillo L, Hernández Avila M, Dubrow R. Chili pepper consumption and gastric cancer in Mexico: a case-control study. Am J Epidemiol. 1994 Feb 1;139(3):263-71.
10. Pabalan N, Jarjanazi H, Ozcelik H. The impact of capsaicin intake on risk of developing gastric cancers: a meta-analysis. J Gastrointest Cancer. 2014 Sep;45(3):334-41.
11. Arora I, Sharma M, Tollefsbol TO. Combinatorial Epigenetics Impact of Polyphenols and Phytochemicals in Cancer Prevention and Therapy. Int J Mol Sci. 2019 Sep 14;20(18):4567.
12. Majidinia M, Bishayee A, Yousefi B. Polyphenols: Major regulators of key components of DNA damage response in cancer. DNA Repair (Amst). 2019 Oct;82:102679.
13. Imran M, Rauf A, Khan IA, Shahbaz M, Qaisrani TB, Fatmawati S, et al. Thymoquinone: A novel strategy to combat cancer: A review. Biomed Pharmacother. 2018 Oct;106:390-402.
14. de Lima RMT, Dos Reis AC, de Menezes APM, Santos JVO, Filho JWGO, Ferreira JRO, et al. Protective and therapeutic potential of ginger (Zingiber officinale) extract and [6]-gingerol in cancer: A comprehensive review. Phytother Res. 2018 Oct;32(10):1885-1907.
15. Mahomoodally MF, Aumeeruddy MZ, Rengasamy KRR, Roshan S, Hammad S, Pandohee J. Ginger and its active compounds in cancer therapy: From folk uses to nano-therapeutic applications. Semin Cancer Biol. 2019 Aug 11:S1044-579X(19)30213-5.
16. Dosoky NS, Setzer WN. Chemical Composition and Biological Activities of Essential Oils of *Curcuma* Species. Nutrients. 2018 Sep 1;10(9):1196.

17. Ghandadi M, Sahebkar A. Curcumin: An Effective Inhibitor of Interleukin-6. Curr Pharm Des. 2017;23(6):921-931.
18. Ismail NI, Othman I, Abas F, H Lajis N, Naidu R. Mechanism of Apoptosis Induced by Curcumin in Colorectal Cancer. Int J Mol Sci. 2019 May 17;20(10):2454.
19. Kunnumakkara AB, Bordoloi D, Harsha C, Banik K, Gupta SC, Aggarwal BB. Curcumin mediates anticancer effects by modulating multiple cell signaling pathways. Clin Sci (Lond). 2017 Jul 5;131(15):1781-1799.
20. Deng YI, Verron E, Rohanizadeh R. Molecular Mechanisms of Anti-metastatic Activity of Curcumin. Anticancer Res. 2016 Nov;36(11):5639-5647.
21. Zhou S, Zhang S, Shen H, Chen W, Xu H, Chen X, et al. Curcumin inhibits cancer progression through regulating expression of microRNAs. Tumour Biol. 2017 Feb;39(2):1010428317691680.
22. Shakeri A, Cicero AFG, Panahi Y, Mohajeri M, Sahebkar A. Curcumin: A naturally occurring autophagy modulator. J Cell Physiol. 2019 May;234(5):5643-5654.
23. Prachayasittikul V, Prachayasittikul S, Ruchirawat S, Prachayasittikul V. Coriander (Coriandrum sativum): A promising functional food toward the well-being. Food Res Int. 2018 Mar;105:305-323.
24. Dutta A, Chakraborty A. Cinnamon in Anticancer Armamentarium: A Molecular Approach. J Toxicol. 2018 Mar 29;2018:8978731.
25. Georgescu SR, Sârbu MI, Matei C, Ilie MA, Caruntu C, Constantin C, et al. Capsaicin: Friend or Foe in Skin Cancer and Other Related Malignancies? Nutrients. 2017 Dec 16;9(12):1365.
26. Ann M. Bode and Zigang Dong. The Two Faces of Capsaicin. Cancer Res. 2011 April 15; 71(8):2809-2814.
27. FAO. FAOSTAT. Food balance sheet. Available from: http://www.fao.org/faostat/en/#data/FBS; last updated December 20, 2020; cited Aug 01, 2020.
28. Global Dietary Database Consortium, Nutrition and Chronic Disease Expert Group (NutriCoDE). Global Dietary Database 1980-2011. [Unpublished]. Available from: https://www.globaldietarydatabase.org/our-data; last updated Jul 30, 2020; cited Aug 01, 2020.
29. FAO. LIFDCs 2018. Available from: http://www.fao.org/countryprofiles/lifdc/en/; last updated Dec 13, 2019; cited Aug 01, 2020.
30. The World Bank. World Bank Country and Lending Groups. Available from: https://datahelpdesk.worldbank.org/knowledgebase/articles/906519-world-bank-country-and-lending-groups; last updated Jul 01, 2020; cited Aug 01, 2020.
31. Schwingshackl L, Schwedhelm C, Hoffmann G, Knüppel S, Laure Preterre A, Iqbal K, et al. Food groups and risk of colorectal cancer. Int J Cancer. 2018 May 1;142(9):1748-1758.
32. Bewick V, Cheek L, Ball J. Statistics review 7: Correlation and regression. Crit Care. 2003 Dec;7(6):451-9.
33. Vieira AR, Abar L, Chan DSM, Vingeliene S, Polemiti E, Stevens C, et al. Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Ann Oncol. 2017 Aug 1;28(8):1788-1802.
34. Millen AE, Subar AF, Graubard BI, Peters U, Hayes RB, Weissfeld JL, et al.. Fruit and vegetable intake and prevalence of colorectal adenoma in a cancer screening trial. Am J Clin Nutr. 2007 Dec;86(6):1754-64.

35. Keum N, Giovannucci E. Global burden of colorectal cancer: emerging trends, risk factors and prevention strategies. Nat Rev Gastroenterol Hepatol. 2019 Dec;16(12):713-732.

FIGURES AND TABLES.

Figure 1. Inclusion-Exclusion Criteria, Data Collection, and Conversion.



C

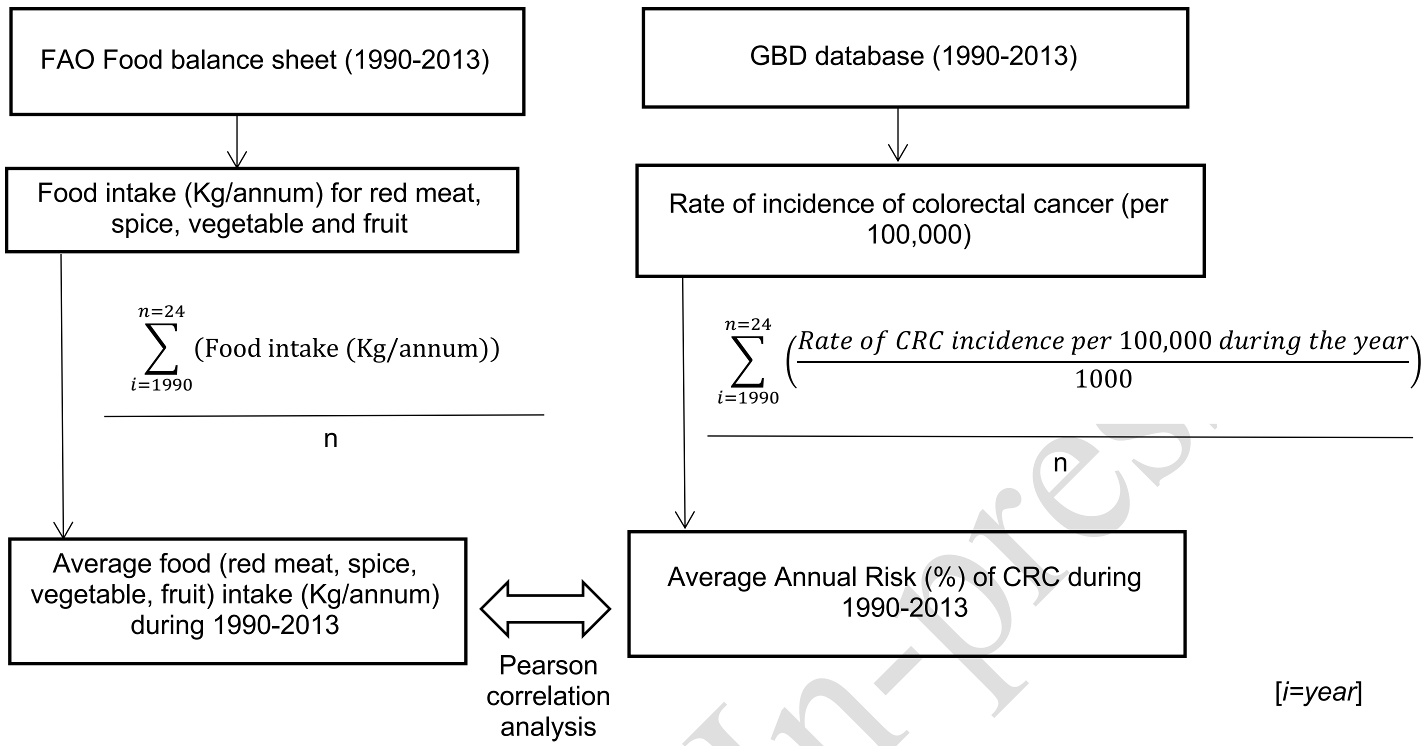

FAO Food balance sheet (1990-2013)
GBD database (1990-2013)
Food intake (Kg/annum) for red meat, spice, vegetable and fruit
Rate of incidence of colorectal cancer (per 100,000)
$\frac{\sum_{i=1990}^{n=24} (\text{Food intake (Kg/annum)})}{n}$
$\frac{\sum_{i=1990}^{n=24} \left(\frac{Rate\ of\ CRC\ incidence\ per\ 100{,}000\ during\ the\ year}{1000}\right)}{n}$
Average food (red meat, spice, vegetable, fruit) intake (Kg/annum) during 1990-2013
Pearson correlation analysis
Average Annual Risk (%) of CRC during 1990-2013
[i=year]

Figure 2. Data Visualisation According to The Ascending Order of CRC Incidence and Food Intake Pattern. **A.** Red meat and processed meat intake (kg/annum) plot shows increasing trend of intake along with increasing cancer risk. **B.** Graph shows a decreasing trend of spice intake (Kg/annum) with increasing CRC incidence.

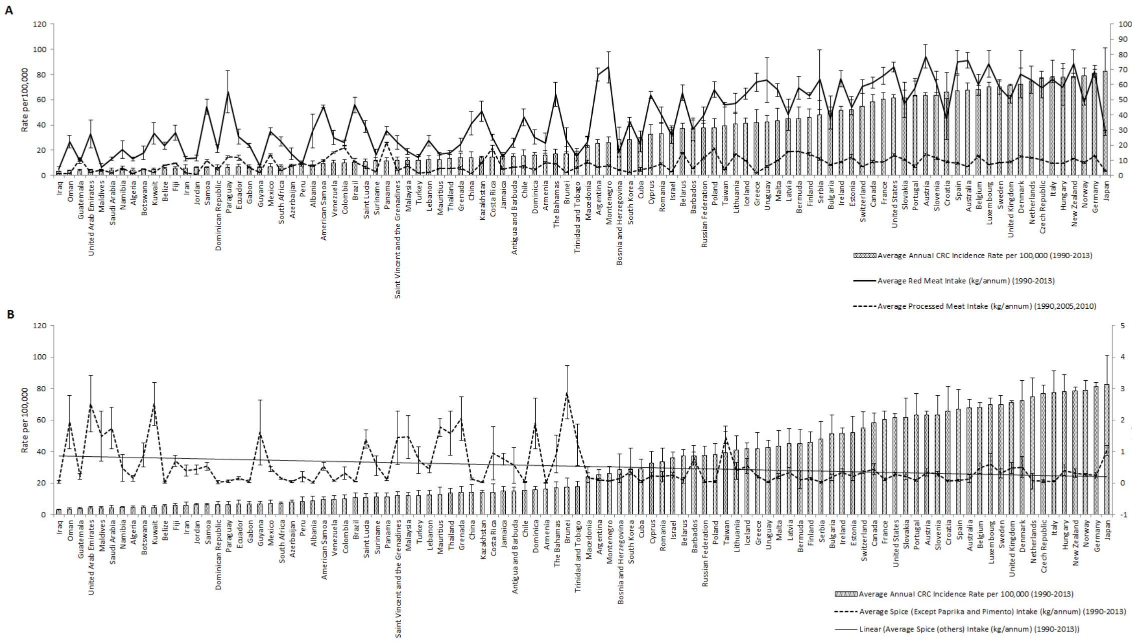


Figure 3. Average Annual Risk (%) of CRC (1990-2013).

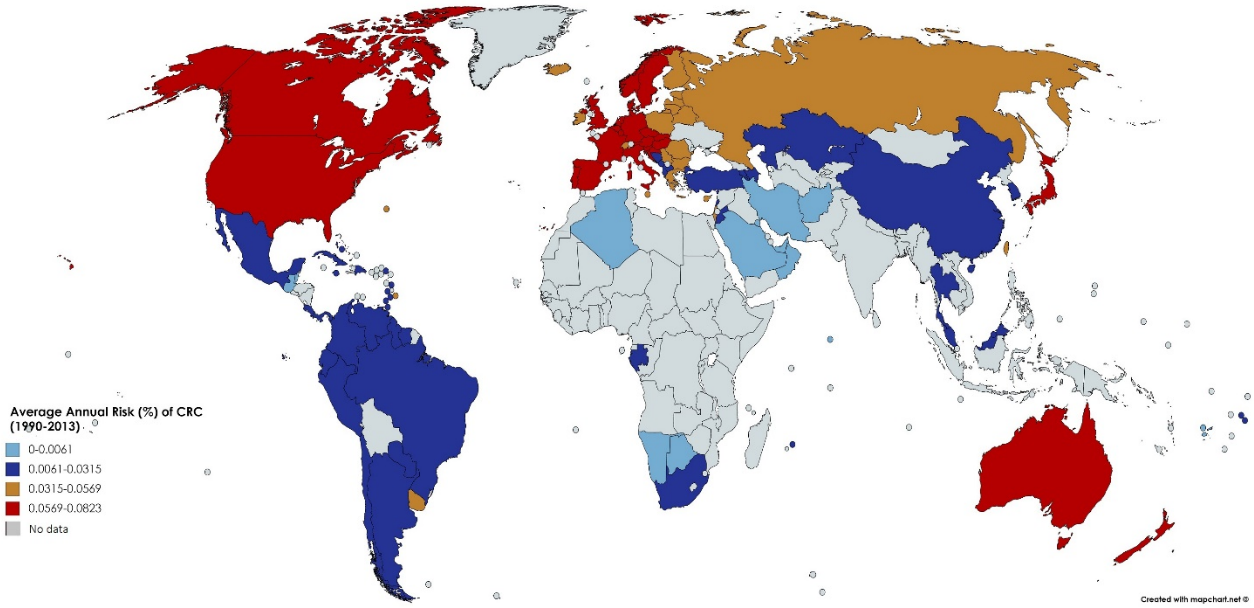


Figure 4. Statistical Analysis of Data Sets. **A-E.** Histogram showing the normal distribution and the skewness of the data. **F.** Boxplots to compare between different dietary intake factors. **G-K.** Dotplot distribution, visualization of correlation analysis with 95%CI along with the corresponding boxplots.

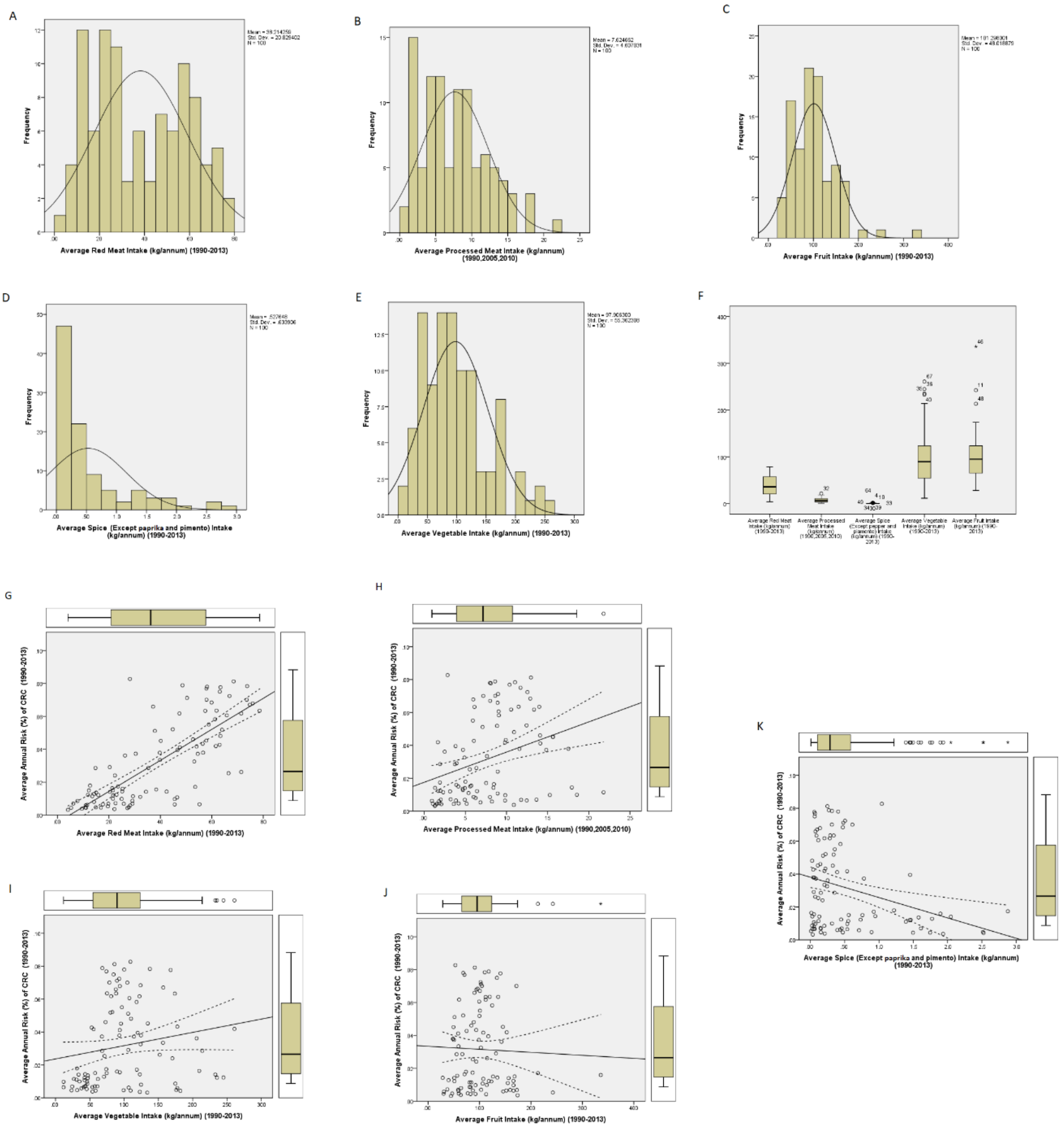


Table 1. Descriptive Statistics .

Descriptive Statistics	Average Annual CRC Incidence Rate per 100,000 (1990-2013)	Average Red Meat Intake (kg/annum) (1990-2013)	Average Processed Meat Intake (kg/annum) (1990,2005,2010)	Average Spice (Except paprika and pimento) Intake (kg/annum) (1990-2013	Average Vegetable Intake (kg/annum) (1990-2013)	Average Fruit Intake (kg/annum) (1990-2013)
Mean	31.567	38.214	7.625	0.528	97.906	101.298
Median	20.996	36.250	7.135	0.285	89.617	95.118
Mode	#N/A	45.571	7.994	0.473	11.713	166.083
Standard Deviation	25.424	20.829	4.607	0.634	55.362	48.019
Kurtosis	-1.113	-1.269	-0.066	2.739	0.437	4.994
Skewness	0.584	0.184	0.621	1.803	0.895	1.543
Range	79.505	74.545	20.854	2.870	249.170	307.264
Minimum	3.215	4.06	0.937	0.008	11.713	28.351
Maximum	82.720	78.605	21.791	2.878	260.882	335.615
Count	100	100	100	100	100	100

Table 2. Results of Pearson Correlation Analysis.

	Average Risk (%) of CRC during the year 1990-2013 (N=100)			
	Pearson Correlation Statistics 'R' (P value - 2 tailed)	95% CI of correlation coefficient*	Regression analysis R square	Regression analysis Unstandardized coeff. (constant, B)
Average Spice Intake (kg/annum) (1990-2013)	*-.301 (***.002***)*	-.470 *to* -.111	.091	(.038, -.012)
Average Red Meat Intake (kg/annum) (1990-2013)	*.772 (***<.001***)*	.678 *to* .841	.596	(-.004, .001)
Average Processed Meat Intake (kg/annum) (1990, 2005, 2010)	*.332 (***.001***)*	.145 *to* .496	.111	(.018, .002)
Average Vegetable Intake (kg/annum) (1990-2013)	.176 (.080)	-.021 *to* .360	_	_
Average Fruit Intake (kg/annum) (1990-2013)	-.035 (.733)	-.23 *to* .163	_	_

Table 3. Results of Partial Correlation Analysis.

	Average Risk (%) of CRC during the year 1990-2013 (N=100)	
	Partial Correlation	P value (2-tailed)
Average Red Meat Intake (kg/annum) (1990-2013) (Controlling for spice and processed meat)	.727	**<.001**
Average Processed Meat Intake (kg/annum) (1990, 2005, 2010) (Controlling for red meat and spice)	-.035	.735
Average Spice Intake (kg/annum) (1990-2013) (Controlling for red meat and processed meat)	-.043	.675

Appendix. Complete dataset of 100 countries

Countries	Average Annual CRC Incidence Rate per 100,000 (1990-2013)	SD	95% CI	Average Red Meat Intake (kg/annum) (1990-2013)	SD	95% CI	Average Processed Meat Intake (kg/annum) (1990,2005,2010)	SD	95% CI	Average Spice (Except paprika and pimento) Intake (kg/annum) (1990-2013)	SD	95% CI	Average Vegetable Intake (kg/annum) (1990-2013)	SD	95% CI	Average Fruit Intake (kg/annum) (1990-2013)	SD	95%CI
Iraq	3.215396	0.187027	0.074825	4.06	1.51006	0.604142	1.287233	0.194183	0.219735	0.034583	0.032966	0.013189	133.7667	15.83252	6.334212	44.37042	13.85853	5.544468
Oman	3.630722	0.655069	0.262078	22.12458	4.135771	1.654623	1.362667	0.06773	0.076643	1.934548	0.837226	0.334954	122.9017	13.05536	5.223136	173.9329	52.187	20.87879
Guatemala	3.828268	0.88075	0.352367	9.469167	1.83184	0.732877	10.88917	0.662385	0.749546	0.207917	0.097668	0.039074	53.78667	10.12561	4.051017	63.56458	7.560836	3.024909
United Arab Emirates	4.256879	0.621881	0.2488	27.18875	9.232612	3.693746	2.075633	0.100115	0.113288	2.524583	0.897988	0.359263	182.0392	78.29899	31.32554	112.8588	24.13625	9.656333
Maldives	4.383584	0.569287	0.227758	5.272083	2.42275	0.969284	3.5916	0.270026	0.305558	1.495833	0.789644	0.315918	58.42292	20.79644	8.320158	82.525	32.0283	12.81375
Saudi Arabia	4.415624	1.583686	0.633595	11.07625	1.07078	0.428394	1.508667	0.091856	0.103943	1.745417	0.657908	0.263213	109.49	17.4012	6.961803	92.16458	6.429159	2.572152
Namibia	4.542243	0.3619	0.144788	16.89708	5.765638	2.306693	5.158667	0.805567	0.911684	0.4725	0.422212	0.168917	23.26083	5.60656	2.243054	30.12292	12.75042	5.101136
Algeria	4.615814	0.973622	0.389523	10.87833	1.15361	0.461533	1.034167	0.21387	0.242013	0.151667	0.093188	0.037282	99.27292	28.40837	11.36551	59.59125	25.40979	10.16585
Botswana	4.71566	0.638017	0.255255	14.90417	4.408264	1.76364	4.185333	0.193977	0.219502	0.89125	0.37659	0.150665	31.50333	6.099098	2.436862	46.79667	10.44	4.176818
Kuwait	4.829733	1.080569	0.43231	27.74083	7.140281	2.856655	1.849333	0.075981	0.085979	2.515	0.683355	0.273394	176.1038	44.00675	17.60604	77.0025	23.83219	9.534686
Belize	5.349731	0.874145	0.349725	19.59167	2.4997	1.000073	6.838883	0.210638	0.238355	0.007917	0.018645	0.00746	45.37917	9.01334	3.606025	242.5279	28.48198	11.39496
Fiji	5.84715	1.155843	0.462425	28.24375	4.92699	1.97117	8.228317	0.173915	0.1968	0.7075	0.177207	0.070896	37.76167	8.23766	3.295692	30.7925	8.94385	3.57822
Iran	5.977376	2.162079	0.864996	11.00792	1.6054	0.642285	1.7885	0.146	0.165212	0.391667	0.178877	0.071565	177.4692	42.50456	17.00505	145.9779	17.18433	6.87504
Jordan	6.249738	0.798187	0.319335	11.55417	2.004032	0.801765	0.936833	0.075981	0.085979	0.43375	0.1412	0.056491	106.62	22.04557	8.819904	59.07792	8.182791	3.273738
Samoa	6.462224	0.485888	0.194392	45.57125	4.918144	1.967631	9.8185	0.683827	0.773809	0.536667	0.122569	0.049037	11.7125	4.97809	1.991742	166.0829	29.49188	11.79899
Dominican Republic	6.514093	2.003954	0.801734	17.67292	2.73586	1.094555	3.8617	0.463837	0.524872	0.029333	0.046031	0.018416	40.96917	10.53231	4.213726	152.1646	41.91734	16.77012
Paraguay	6.543785	1.975854	0.790492	55.21625	14.05493	5.623043	12.45623	0.639452	0.723595	0.059583	0.036651	0.014663	53.71	5.84574	2.338743	87.1225	10.84585	4.339168
Ecuador	6.881445	2.259339	0.903907	25.77083	4.9124	1.965336	11.77733	1.721444	1.947961	0.152083	0.045203	0.018085	24.31292	3.47583	1.390599	172.6671	35.10543	14.04484
Gabon	6.907452	1.38702	0.055491	19.78667	1.152285	2.061306	4.936017	0.209878	0.237495	0.057083	0.046296	0.018522	42.77542	2.530377	1.012343	159.5242	12.32892	4.932506
Guyana	6.984883	1.445769	0.578418	6.13625	1.01875	0.407577	2.017233	0.294506	0.333259	1.611667	1.032029	0.41289	61.09	26.76844	10.70941	58.31875	14.62383	5.850643
Mexico	6.99866	2.254706	0.902054	29.16417	2.406061	0.998614	13.63762	0.429668	0.486206	0.455833	0.079231	0.031698	57.21875	8.302557	3.321654	103.0113	8.185045	3.27464
South Africa	7.217742	0.930488	0.372266	22.575	2.931427	1.172794	3.212	0.2555	0.28912	0.146667	0.018098	0.007241	43.69625	1.67294	0.745426	37.34292	3.534968	1.414256
Azerbaijan	8.025994	1.027961	0.411262	14.20636	3.7835	1.513691	6.2415	0.381071	0.431215	0.051364	0.030752	0.012303	124.6091	48.5804	19.43583	64.04591	12.07202	4.829729
Peru	8.573027	2.768548	1.10763	7.75625	0.658673	0.263519	7.9935	1.676221	1.896787	0.202083	0.158881	0.063585	46.40958	13.49941	5.400788	82.83167	20.59955	8.241386
Albania	8.649495	2.887788	1.15137	29.1375	11.12194	4.449624	6.003033	0.49201	0.556752	0.02375	0.022227	0.008892	174.6917	44.4348	17.77732	80.71417	40.87856	16.35453
American Samoa	9.72594	1.596476	0.638712	45.57125	0.975989	1.967631	9.842833	0.704302	0.796978	0.536667	0.122569	0.049037	11.7125	4.9784	1.991742	166.0829	29.49187	11.79899
Venezuela	9.813441	2.422984	0.969377	24.94875	4.739534	1.896174	15.2643	0.456119	0.516137	0.0725	0.02111	0.008446	45.94667	11.78388	4.714448	92.2275	16.26074	6.505534
Colombia	9.9474	2.621819	1.048927	21.58042	1.73974	0.696031	18.55417	0.877013	0.992416	0.314167	0.187592	0.075051	34.96292	5.48054	2.192633	114.1579	17.87125	7.149861
Brazil	10.76841	2.936873	1.174973	46.54583	5.054275	2.022094	8.9206	0.230297	0.260601	0.050417	0.009546	0.003819	42.44417	6.737394	2.69547	106.0017	14.31536	5.727234
Saint Lucia	11.06218	2.112933	0.845334	32.16667	3.877501	1.551295	5.3874	0.800948	0.906342	1.391818	0.28758	0.112325	30.52833	7.75223	3.101481	154.9404	47.36682	18.95033
Suriname	11.4538	2.355061	0.942203	13.5125	3.66777	1.467361	2.311667	0.075981	0.085979	0.552083	0.318993	0.127621	61.80458	12.41501	4.966946	83.86542	14.84489	5.939084
Panama	11.46004	2.389865	0.956128	29.34917	2.762925	1.10538	21.7905	0.160562	1.313276	0.117083	0.039506	0.015805	26.89583	2.104841	0.842096	80.65625	7.582238	3.033471
Saint Vincent and the Grenadines	12.02733	2.616272	1.046707	21.655	4.46904	1.787956	3.139	0.1591	0.180035	1.447917	0.84479	0.33798	47.11042	16.05531	6.423345	123.0329	53.93002	21.57611
Malaysia	12.18671	1.764496	0.705933	15.85708	2.037936	0.81533	6.424	0.790451	0.894472	1.4625	0.677743	0.271022	42.29667	13.85094	5.541427	51.07042	3.803892	1.521846
Turkey	12.2755	2.910896	1.164548	11.80792	1.97162	0.788798	1.706983	0.051143	0.057873	0.732083	0.422786	0.169146	235.4583	14.14981	5.661	117.8967	6.362656	2.545546
Lebanon	12.37531	2.978815	1.191752	22.94773	3.508004	1.403468	1.9637	0.199598	0.225862	0.4475	0.124874	0.049959	244.9183	54.05147	21.6247	165.8821	58.91908	23.57211
Mauritius	12.84393	4.460557	1.784562	14.27792	0.88076	0.352371	4.696333	0.075981	0.085979	1.773333	0.289041	0.115631	70.70708	12.57732	5.031883	39.825	12.61934	5.048694
Thailand	13.63332	3.130167	1.252305	15.04958	1.37096	0.548489	4.684167	0.237484	0.268733	1.577083	0.69986	0.279997	47.14417	5.246407	2.098961	107.3354	15.14444	107.3354
Grenada	14.10119	3.720599	1.488522	20.38167	4.259786	1.704238	4.939667	0.793263	0.897645	2.0475	0.693035	0.277267	33.59583	6.529158	2.612159	156.6225	20.58307	8.234794
China	14.17118	4.750704	1.900643	34.40417	7.569641	3.028432	1.314	0.073	0.082606	0.129583	0.025105	0.010044	232.9733	83.64308	33.46359	50.68542	23.21748	9.288757
Kazakhstan	14.26532	1.02893	0.41165	42.42636	6.600705	2.640784	8.419333	0.400392	0.453078	0.0275	0.021518	0.008609	122.9532	55.42999	22.17621	28.35091	24.62872	9.853361
Costa Rica	14.40892	5.011934	2.005154	25.1625	1.831182	0.732612	17.93975	1.939133	2.194295	0.945833	0.853168	0.341338	43.10333	7.53856	3.015997	134.5954	28.034	11.21573
Jamaica	15.03068	2.99102	1.196635	12.21042	1.446084	0.578544	4.148833	0.258953	0.293027	0.75875	0.19342	0.077383	74.60667	13.80655	5.523671	126.2396	19.07445	7.63123
Antigua and Barbuda	15.09076	2.13994	0.856139	21.57833	2.806167	1.12268	5.589367	0.146743	0.166053	0.558333	0.563704	0.225524	57.71583	14.06844	5.628446	168.0733	24.126	9.65227
Chile	15.54044	4.593486	1.837743	38.37792	5.710631	2.284686	5.718333	0.796695	0.901438	0.052083	0.011025	0.004411	93.66	15.8243	6.330923	56.53	5.940095	2.37649
Dominica	15.97081	2.003954	1.082912	25.31333	4.730183	1.892433	3.9055	0.348188	0.394004	1.895417	0.809138	0.323717	89.65417	15.25563	6.103412	335.615	46.03415	18.41716
Armenia	16.39675	3.571297	1.42879	21.25818	6.65543	2.662681	8.469217	0.651669	0.737419	0.012273	0.011098	0.00444	209.5009	91.62975	36.65887	70.83818	27.89445	11.1599
The Bahamas	17.11654	3.523952	1.409848	53.56	7.925146	3.17066	7.523867	0.177929	0.201342	0.923333	0.601199	0.240525	118.4333	48.58034	4.569895	213.4879	74.02359	29.61506
Brunei	17.41289	5.643852	2.25797	23.53625	7.783558	3.114015	1.911383	0.018005	0.020374	2.878333	0.850763	0.34037	74.00333	13.95592	5.579027	86.44583	10.1428	4.057907
Trinidad and Tobago	17.92963	3.287277	1.315161	12.65042	3.220444	1.288422	5.009017	0.62119	0.70293	1.21875	0.656654	0.262711	31.17	4.688104	1.875598	73.58583	17.64674	7.060035
Macedonia	24.06282	6.331517	2.533088	22.31455	3.561769	1.424978	8.929117	0.911801	1.031781	0.17625	0.156672	0.062681	170.3618	22.10073	8.841972	93.60545	15.85572	6.343495
Argentina	25.44668	3.185324	1.274372	66.51625	4.21215	1.564523	5.535833	0.264048	0.298792	0.112917	0.031551	0.012623	71.32917	4.212159	1.685184	86.96375	13.35529	5.343131
Montenegro	26.19496	4.490184	1.796415	71.45857	10.17644	4.07135	6.338833	0.444302	0.502765	0.06875	0.013562	0.005426	151.8841	61.46676	24.59137	114.6527	48.10625	19.24616
Bosnia and Herzegovina	28.57631	9.720817	3.889065	14.77	2.42375	0.969686	3.723	0.411334	0.46546	0.151667	0.140827	0.056341	67.85241	25.73069	10.29423	55.32542	33.94101	13.57899
South Korea	28.63192	13.57889	5.432587	35.33375	2.931427	3.298644	1.922333	0.2555	0.242013	0.35125	0.092657	0.03707	213.9479	12.1905	4.877126	66.48417	7.028134	2.811788
Cuba	29.13199	6.23338	2.493826	20.30708	4.734964	1.894346	3.935917	1.16069	1.313421	0.049167	0.036106	0.014445	106.11	51.3527	20.545	132.0292	28.6499	11.46217
Cyprus	32.58557	7.616522	3.047188	53.1675	2.300456	0.920357	4.891	0.1591	0.180035	0.241667	0.087361	0.034951	124.0525	13.458	5.384247	102.5746	18.73154	7.494039
Romania	33.45477	8.655354	3.462799	39.85083	5.316256	2.126906	7.6285	0.738167	0.835299	0.204167	0.167278	0.066924	156.6938	26.65165	10.66269	59.07583	10.48543	4.19497
Israel	36.17458	3.366656	1.346918	26.25625	5.209916	2.084363	2.484433	0.113464	0.128394	0.250417	0.099716	0.039894	205.6771	31.0872	12.43728	142.7008	20.02633	8.012054
Belarus	37.24889	4.195419	1.678486	54.55773	5.096129	2.038839	14.83117	0.117331	0.13277	0.08	0.094685	0.037881	114.1927	28.36355	11.34757	50.15273	16.21216	6.486096
Barbados	37.3024	6.669154	2.668168	30.42375	7.368597	2.947999	4.709717	0.147377	0.16677	0.780833	0.205573	0.082245	67.595	14.22956	5.692904	98.69417	19.34899	7.741067
Russian Federation	37.88647	5.418214	2.167697	39.76625	5.316256	2.968048	11.5705	0.641611	0.726038	0.055455	0.038758	0.015506	93.10208	13.68463	5.474894	48.78083	14.95845	5.984519
Poland	37.93213	7.032733	2.813628	56.61417	5.19815	2.079655	17.51878	0.467205	0.528682	0.040833	0.03256	0.013026	124.5188	9.377719	3.7518	48.15542	7.220692	2.888826
Taiwan	39.53447	16.57116	6.629723	46.63875	1.639274	0.655834	3.808167	0.326187	0.369108	1.453333	0.199666	0.079882	119.7479	10.72564	4.291069	116.9133	6.120582	2.448698
Lithuania	41.18739	8.766126	3.507116	47.60091	6.597727	2.639592	14.11333	0.243029	0.275008	0.389091	0.26009	0.104056	93.65864	15.4069	6.163931	58.37318	20.96649	8.38819
Iceland	41.69011	3.631964	1.453062	54.07125	3.624894	1.450233	9.806333	0.21387	0.242013	0.535	0.239329	0.09575	55.52625	13.89924	5.558033	107.2217	22.52269	9.01079
Greece	41.92193	10.33252	4.133792	61.56792	6.117708	2.447548	1.654667	0.021073	0.023846	0.204167	0.039663	0.015868	260.8821	23.63483	9.455726	152.8013	19.62221	7.850376
Uruguay	42.7233	4.562272	1.825255	63.02958	14.72479	5.891036	6.034667	0.717421	0.811823	0.040833	0.016659	0.006665	52.68792	8.518392	3.408004	74.81375	13.33048	5.333205
Malta	43.31447	9.906547	3.963371	56.46292	4.293066	1.717553	9.915833	0.210733	0.238462	0.2175	0.0829	0.033186	177.5808	35.7703	14.31085	93.40208	10.23264	4.093837
Latvia	45.09555	9.283097	3.713944	40.17227	10.30445	4.122566	15.63052	0.243139	0.275132	0.325455	0.164743	0.06591	95.43818	15.22671	6.091843	49.32909	8.623573	3.450085
Bermuda	45.22684	9.008846	3.604223	57.83833	7.67069	3.068861	15.6531	-	-	0.107917	0.269927	0.107991	134.5458	26.61447	10.64781	145.4092	59.17804	23.67571
Finland	46.03903	6.55217	2.621366	52.7025	2.03973	0.816048	14.07683	1.11376	1.260315	0.14375	0.04332	0.017331	72.88792	8.900822	3.561005	84.03417	11.09396	4.438429
Serbia	48.09135	11.12415	4.450505	63.34455	19.70517	7.883565	10.9135	0.935568	1.058676	0.025	0.027819	0.01113	110.0686	12.75014	5.101025	88.84864	21.1665	8.468209
Bulgaria	51.16442	11.89936	4.76065	37.86625	7.305592	2.922792	7.090733	0.331374	0.374978	0.182917	0.11059	0.044245	105.875	29.17153	11.67083	51.32125	13.519	5.408643
Ireland	51.85008	3.139783	1.256152	63.97583	5.36864	2.147864	8.8476	0.449232	0.508344	0.33875	0.124003	0.04961	80.17917	8.13688	3.255373	99.78583	35.37126	14.15119
Estonia	52.13943	10.25427	4.102486	44.82727	4.937399	1.975335	12.43433	1.427394	1.615219	0.22	0.133514	0.053416	82.76909	2.498754	8.413452	68.08455	16.22583	6.491566
Switzerland	55.06131	10.09552	4.038974	58.80917	4.50618	1.802817	5.913	0.246395	0.278817	0.355	0.04086	0.016347	96.73708	6.486944	2.595271	100.7171	17.4706	6.989567
Canada	58.2536	5.991079	2.396887	61.27583	3.7252	1.490395	9.076333	0.706191	0.799116	0.437083	0.174168	0.069681	118.115	5.018839	2.007917	124.5038	8.533739	3.414144
France	60.6062	5.16175	2.065092	65.83875	5.563897	1.42583	9.039833	0.075981	0.085979	0.114167	0.045389	0.18159	107.6683	9.02145	3.609269	99.26917	12.82443	5.130747
United States	61.73339	2.254575	0.902001	71.43792	3.27675	1.31095	13.34683	0.988175	1.118205	0.282083	0.066068	0.026432	122.4183	6.43317	2.573758	111.9371	6.481988	2.593288
Slovakia	61.75994	12.20574	5.043252	47.41381	9.01762	3.856829	10.56067	0.423043	0.47871	0.204286	0.08594	0.034383	81.12143	12.49067	5.342254	60.18381	8.557251	3.659929
Portugal	63.34892	13.55222	5.421916	57.46292	5.03406	2.014007	6.107667	0.689966	0.780759	0.088333	0.022968	0.009189	173.9204	21.25104	8.502031	111.8267	8.268197	3.307907
Austria	63.43816	2.190147	0.876225	78.60542	7.742725	3.097678	13.9795	0.38628	0.437109	0.339167	0.112969	0.044876	88.39292	13.83624	5.535549	136.145	18.64579	7.459734
Slovenia	63.47901	12.14897	4.860512	61.82909	7.032669	2.813602	11.47317	0.843721	0.954743	0.288182	0.0696	0.027845	75.01045	9.623377	3.850082	119.7295	28.64017	11.45824
Croatia	65.91835	15.59634	6.239722	37.16682	13.40318	5.362288	8.91695	0.802975	0.908635	0.072727	0.026936	0.010776	87.93091	17.30954	6.925134	90.04864	13.98168	5.593735
Spain	67.06038	12.34562	4.939547	74.80583	7.600083	3.040611	8.0154	0.503277	0.569501	0.09625	0.03076	0.012306	157.0733	19.51131	7.806007	100.5733	17.04515	6.819356
Australia	67.91454	5.204565	2.082222	75.94208	5.170801	2.068713	5.959233	0.077457	0.087649	0.139583	0.120271	0.048117	93.72417	6.866944	2.7473	93.91625	7.190426	2.876717
Belgium	68.42393	2.745958	1.098592	59.91833	6.854452	2.742302	12.88815	0.352447	0.398824	0.4725	0.171851	0.068753	123.9496	11.01645	4.407415	96.31958	29.055	11.62421
Luxembourg	70.04707	3.819448	1.528069	73.60167	8.804434	3.522442	7.178333	0.237484	0.268733	0.611429	0.330963	0.13241	104.6467	10.9893	7.745267	171.6917	19.26215	17.2729
Sweden	70.08949	5.645858	2.258772	57.94625	4.585853	1.83469	8.622517	0.273198	0.309147	0.3125	0.152864	0.061157	78.51208	10.9084	4.364188	104.5067	14.532	5.813904
United Kingdom	71.20889	1.19837	0.479439	50.35583	2.57364	1.029655	8.970483	0.55806	0.631493	0.479583	0.174093	0.069651	89.58	4.994628	1.99823	102.7788	22.84934	9.141474
Denmark	72.38548	12.84028	5.137088	66.88083	15.6642	6.266872	12.54383	0.339142	0.383769	0.50375	0.327757	0.131128	92.82375	15.42533	6.171306	102.0617	27.4508	10.98241
Netherlands	75.0161	11.52739	4.611831	63.11917	8.92277	3.569786	11.70433	0.54912	0.621376	0.062167	0.24266	0.097083	84.66167	11.39422	4.558554	133.7042	18.33496	7.335378
Czech Republic	76.86999	5.493098	2.197656	57.87714	6.7967	2.719197	10.36843	0.318207	0.360078	0.065417	0.048363	0.019349	74.20429	3.649078	1.459909	70.68429	6.325502	2.530682
Italy	77.70753	13.4038	5.362539	63.38167	2.012054	0.804975	8.090833	0.223019	0.252365	0.056667	0.023529	0.009413	167.8567	18.59969	7.441287	140.5983	14.92942	5.972903
Hungary	77.97411	10.87011	4.348869	58.155	12.22348	4.89032	7.9935	0.348188	0.394004	0.404583	0.166524	0.066622	100.0633	13.8574	5.544035	68.265	9.858151	3.944009
New Zealand	78.36652	2.423159	0.969448	73.73667	9.193866	3.678245	11.03273	0.135313	0.153118	0.313333	0.128085	0.051246	137.565	26.04198	10.41877	110.1063	9.683861	3.87428
Norway	78.85214	6.137159	2.45533	48.615	2.086953	0.83494	8.614	0.568979	0.643848	0.267917	0.043736	0.017498	68.1825	8.260081	3.30466	117.8171	17.88359	7.154794
Germany	81.2474	2.609038	1.040973	68.50375	4.081449	1.63289	12.96967	0.372824	0.421883	0.24625	0.075976	0.030396	85.88917	6.798588	2.719952	90.75917	10.93998	4.376823
Japan	82.71998	18.51557	7.407635	28.18042	1.700893	0.680487	2.838483	0.108543	0.122825	1.041667	0.156363	0.062255	109.145	5.69395	2.278016	52.94792	3.24117	1.296714