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1 Article

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2 Predicting future cancer burden in the United States 3 by artificial neural networks

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Abstract: The prediction of future cancer burden represents a key element for the design of cancer control programs and for the allocation of economic resources in the health system. To capture the complex relationships between risk factors and cancer incidences in the United States, we adopted an artificial neural network (ANN) algorithm. Data on the incidence of the four most common tumors (breast, colorectal, lung and prostate) from 1992 to 2013 (available from National Cancer Institute online datasets) were used for training and validation and data until 2050 were predicted.

- According to our predictions, the rapid decreasing trend of prostate cancer incidence started in 2010 will continue until 2018/2019 and then it will slow down and reach a plateau after 2050, with several differences among different ethnicities. The incidence of breast cancer will reach a plateau in 2030, while colorectal cancer incidence will reach a minimum value of 30/100.000 in 2025, followed by a plateau in 2030 in men and in 2050 in women. As for lung cancer, the incidence will decrease from 53/100.000 (2015) to 42/100.000 in 2030 and 32/100.000 in 2050.
- 40 This up-to-date prediction of cancer burden in the United States could be a crucial resource for 41 planning and evaluation of cancer-control programs. Urgent global actions towards a dramatic 42 reduction of cancer-related risk-factors are actually needed and will accelerate the drop of 43 incidences and the route to cancer eradication in future years.
- Keywords: Artificial Neural Network; Breast cancer; Colorectal cancer; Future tumor burden; Lung cancer;
 Prostate Cancer.
- 46
- 47 **1. Introduction**

48 Cancer represents the second most lethal disease condition in the US, with more than 1,600 49 deaths per day and an estimated total that will exceed 600,000 Americans in 2018 [1]. The number of 50 new diagnoses has progressively increased in the last decades getting over 1,700,000 new cases 51 estimated in the US in 2018 [1]. However, it is important to note that in the last 25 years the rate of 52 cancer-related deaths has declined for the four types of tumor with the highest incidences (prostate, 53 breast, colorectal and lung) [1]. This event can be explained through both (1) the advances obtained 54 by introduction of molecularly targeted drugs and novel immunotherapies as well as (2) the 55 development of more effective diagnostic techniques and (3) the downward trend of cancer-related 56 risk factors, above all smoking attitude.

57 The predictions of incidence cancer rates could be very useful to optimize the allocation of finite 58 resources, the key elements of cancer control in next years and the future planning of cancer control 59 programs. This has become rapidly fundamental due to the rising costs of oncologic treatments 60 approved by the US Food and Drug Administration (FDA) in the last decades [2–5]. The trends of 61 population growth and the ageing represent crucial factors for predicting the future burden of cancer, 62 as the majority of tumors is age-dependent [6]. Furthermore, we might attempt to estimate the future 63 incidence of different tumor types basing on the plausible changes of the risk patterns over time.

64 Previously, several prediction techniques have been employed to estimate future cancer trends. 65 These methods include: linear extrapolation of trends [7,8], simple linear Poisson models [9,10] and 66 classical [6, 11] or Bayesian age-period-cohort models [12]. However, the limits of these techniques 67 [13] have led to the research of more accurate prediction models. To capture the complex 68 relationships between input and target variables, we adopted an artificial neural network (ANN) 69 algorithm. This mathematical model imitates the human brain strategy to solve problems and is able 70 to extract knowledge directly from the raw data. These non-parametric modeling algorithms are very 71 flexible and can perform any complex function mapping. Since ANN algorithms can train themselves 72 under various circumstances, they are used in various fields, from finance to medicine [14-17]. In this 73 study, we estimated the incidences of the four most frequent cancer diseases (prostate, breast, 74 colorectal and lung) by developing an ANN algorithm to predict the number of new cases in the US 75 till 2050.

77 2. Materials and methods

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2.1 Data sets

80 USA population and USA life expectancy data derived from Gapminder (www.gapminder.org). 81 Observed and projected obesity data in USA for male and female come from work of Wang et al. [18]. 82 Number of cancer cases from 1975 to 2013 in USA was obtained by National Cancer Institute 83 (https://progressreport.cancer.gov/diagnosis/incidence). We extracted data about tobacco 84 consumption in developed countries derived from the work of Ng et al. [19]. Note that the best fitting 85 polynomial to predict and interpolate missing data was Y = -0.3737 * X^2 – 3.7956 * X + 2363, where 86 X is the year and Y the tobacco consumption.

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2.2 Implementation of Artificial Neural Networks

Four ANNs, one for each cancer type, were built. To predict future incidence of prostate cancer in USA, we considered the three main risk factors internationally recognized: (1) demographic trend, (2) life expectancy data and (3) race/ethnicity [20–22]. Since the output also depends on race/ethnicity, we retrained this ANN with prostate cancer cases of White, Black, Hispanic, Asian/Pacific Islander and American Indian/Alaska Native races. Our predictions did not include prostate cancer with positive family history due to the lack of historical series in this setting. Data from 1992 to 2013 were used for training and validation and data from 2014 to 2050 were predicted.

Age is a commonly known factor associated with the risk of breast cancer [23]. It is estimated that females who survive till 85 years will present a lifetime rate of approximately 11% of developing breast cancer [23]. Similarly, obesity is associated with an increased risk of both premenopausal [24] and postmenopausal breast cancer [25], being also associated with worse cancer-related survival in all breast cancer subtypes. To predict the incidence of breast cancer in USA, our ANN was based on
(1) demographic trend, (2) life expectancy data and (3) obesity. Data from 1992 to 2013 were used for
training and validation and data from 2014 to 2050 were predicted. As for prostate cancer, here we
considered total population as an input variable.

The risk of developing colorectal cancer increases with age, with more than 90% of cases occurred in patients who are 50 years old or older [26]. It has been estimated that 29.5% of colorectal cancers can be attributable to a Body Mass Index (BMI)>22.5 [27], with an incidence that results different between men and women [28]. To predict the future incidence of colorectal cancer in USA, we included (1) demographic trend, (2) life expectancy data and (3) obesity as inputs of the ANN algorithm. Data from 1975 to 2013 were used for training and validation and data from 2014 to 2050 were predicted.

111 The vast majority of lung cancers can be attributable to tobacco attitude, with over 80% of lung 112 tumors related to smoking [29]. As an indirect measure of exposure to pulmonary carcinogens 113 (ionizing radiation, radon gas, etc), age can be considered as a predictive factor of lung cancer in both 114 smokers and never-smokers patients [30]. Indeed, the relationship between age and lung cancer in 115 non-smokers has been widely reported [31-33]. To predict the future incidence of lung cancer in USA, 116 we considered (1) demographic trend, (2) life expectancy data and (3) smoking prevalence as input 117 variables. Data from 1975 to 2013 were used for training and validation and data from 2014 to 2050 118 were predicted.

119 As a forecasting model we used multilayered perceptrons (MLP), a layered feed forward 120 network that is trained by back propagation algorithm. Generally, a perceptron has several inputs 121 and one output and the function connecting inputs and output is nonlinear. A back propagation 122 training algorithm adjusts the connection strength between adjacent nodes. This method is easy to 123 use, and it can model any kind of data although for training it takes longer time than other methods 124 and it requires large amounts of training data. The flow of the algorithm that we used in this paper 125 is showed in FigureS1. In order to obtain the best scores, the network structure and its internal 126 parameters, hidden neuron number and transfer functions, the learning rate (LR) and learning 127 momentum (LM) have been determined by many trials according to the trial-and-error method. 128 Performance of each topology was assessed by the Mean Square Error and the Regression values. We 129 sought to reach the best results by minimum number of nodes to avoid that the ANN memorized 130 data rather learning them for generalization. Our ANNs are constructed with three layers, the input 131 layer has as many neurons as inputs and the output layer has one neuron. The ANNs for colorectal, 132 lung, breast and prostate cancers have respectively 10, 25, 20 and 20 neurons that implement the 133 "tansig" function in the hidden layer. Software package Matlab R2014b (Mathworks Inc.) was used 134 in this study. Inputs were scaled, by "mapminmax" function of Matlab, to fall in between -1 and 1 in 135 order to account for different variations and degrees of magnitude of input variables. We used 70% 136 of the data for training and 30% for validation and these data sets were chosen randomly. 137

3. Results

138 139

140 *3.1 Prostate cancer*

141 The incidence of prostate cancer has decreased from an incidence of 200 cases/100.000 habitants 142 registered in the 1990s in USA to less than 150/100.000 in 2010 and, according to our predictions, will 143 successively fall under 50/100.000 from 2025 (Figure 1A). As for all the different races/ethnicities, our 144 algorithm predicts that the rapid decreasing trend started in 2010 will continue until 2018/2019 and 145 then it will slow down and will reach a plateau after 2050 (Figure 1A). The trend observed in the 146 overall population reflects that reported in white patients, characterized by an incidence of less than 147 200/100.000 cases in the 1990s, with a drop under 50/100.000 in 2020s (Figure 1B). The incidence is 148 superior in black patients (Figure 1C), who have been associated with an incidence lower that 149 200/100.000 only from 2012 and will reach a value of less than 50/100.000 only more than ten years 150 later (Figure 1C). Otherwise, patients with Asian/Pacific ethnicity as well as American Indian and

Figure 1. Trend and predicted new cases of prostate cancer overall (A) and by ethnicity (B=White; C=Black; D=Hispanic; E=Asian/Pacific Islander; F=American Indian/Alaska Native).



156 157

158 The fading in prostate cancer decreasing from 2018 could reflect the fading in life expectancy 159 and population increasing. The racial disparities are caused by behavioral differences and unequal 160 access to high-quality health care but this gap is rapidly reducing.

- 161 162
- 3.2 Breast cancer

The incidence of breast cancer has slightly decreased from 1990s (133 cases/100.000 habitants), registering a drop to 125/100.000 in 2002 and to 124/100.000 in 2015 (Figure 2). Based on our prediction algorithm, the incidence will decrease to 123/100.000 in 2020, reaching a plateau in 2030 (Figure 2). Performance of Train and Validation phases (Figure S3) showed that, in this setting, the ANN algorithm obtained worst predicting results (Performance of Train = 0.641; Validation phases = 0.577) compared to prostate, colorectal and lung cancer. The reasons of this different behavior are discussed in the next sections.

170

171 Figure 2. Trend and predicted new cases of breast cancer. Our calculations are based on172 population, life expectancy and obesity data for female.

173



3.3 Colorectal cancer

The incidence of colorectal cancer has progressively increased from 1970s (60 cases/100.000 habitants), registering its maximum in 1985 (66/100.000) (Figure 3A). From late 1980s, the downward trend led an incidence of 55/100.000 in 2000, with a progressive reduction to 35/100.000 in 2015 (Figure 3A). Based on our prediction algorithm, the incidence will reach a minimum value of 30/100.000 in 2025, followed by a plateau until 2050 (Figure 3A).

Due to the influence of gender on colorectal cancer incidence [33], we further predicted the incidence in males (Figure 3B) and females (Figure 3C). We found that the incidence was maximum for men in 1985 (79/100.000) and for women in 1985 (57/100.000), respectively (Figure 3B, 3C). Interestingly, we predicted that the reduction of the incidence trend will lead to a plateau around 30/100.000 in 2030 in men, while women will be associated with a lower incidence that will drop below 20/100.000 in 2050 (Figure 3B, 3C).

188

189 **Figure 3.**Trend and predicted new cases of colon cancer overall (A) and by gender (B=males;

C=females). Our calculations are based on population, life expectancy and obesity for males andfemales.



193 104 - 2.4 Luna a

194 *3.4 Lung cancer*

The incidence of lung cancer has progressively increased from 1970s (53 cases/100.000 habitants), registering its maximum in 1992, characterized by 69/100.000 (Figure 4A). From 1990s, the downward trend in the smoking attitude has led to a gradually reduction of new cases of lung cancer, with an incidence in 2015 comparable to 1970s (53/100.000) (Figure 4A). Based on our prediction algorithm, the incidence will decrease to 42/100.000 in 2030 and fall to 32/100.000 in 2050 (Figure 4A).

Due to the different time-trends in tobacco consumption, we further predicted the incidence in males (Figure 4B) and females (Figure 4C). While the maximum incidence was registered in 1984 for males (102/100.000), the highest value (54/100.000) for women was reported in 2005 due to the rapid increase of smoking prevalence among women about 20 years later than men (Figure 4B, 4C). Interestingly, the drop of the incidence trend appears slower in males than in females, reaching a plateau beyond 2050 (25/100.000), 15 years after the plateau predicted for females (28/100.000) (Figure 4B, 4C).

Figure 4. Trend and predicted new cases of lung cancer overall (A) and by gender (B=males; C=females). Our calculations are based on population, life expectancy and smoking data for males

210 and females.







225

3.5 Regression Analysis

214 The ANN outputs with respect to targets for training and validation sets are shown in scatter 215 plots (Figures S2-S5). The dashed line represents the perfect result, i.e.: outputs = targets. The solid 216 line depicts linear best fit between the outputs and the targets. The R-value summarizes the 217 relationship between the outputs and targets. In particular, if R=1 there is an exact linear relationship 218 between outputs and targets. If R is close to zero means that a no linear relationship links outputs to 219 targets. In almost all our models, apart for breast cancer and prostate cancer in American 220 Indian/Alaska Native Races, the R-values around 0.9 or greater indicate a reasonably good fit for a 221 data set. Analogously, a very small value of mean square error (MSE) suggests the goodness of the 222 models. 223

4. Discussion

The lifetime risk of developing cancer is related, in general, to a longer life expectancy. However, a range of influences, from environmental and attitude changes to prevention campaigns, screening programs and innovation technologies, should be taken into account in order to increase the accuracy of predicting models for cancer incidence. 230 Among the four most frequent tumor types we showed a general decline in the incidences in the 231 United States. The changes in prostate cancer incidence observed in the late 1980s and early 1990s 232 (Figure 1A) were probably due to the introduction of widespread prostate-specific antigen (PSA) 233 testing that allowed the detection of asymptomatic disease [34]. The reduction in prostate cancer 234 incidence from 2010 to 2013 can be attributed to decreased PSA testing. In fact, the US Preventive 235 Services Task Force (USPSTF) diffused a recommendation about the use of PSA as a screening method 236 for prostate cancer. The task force, basing on data from Prostate, Lung, Colorectal and Ovary cancer 237 screening study (PLCO) and the European Randomized Study of Screening for Prostate Cancer 238 (ERSPC) trial, informed that the potential harms of testing (erectile dysfunction, incontinence and 239 serious surgical complications) overcame the benefits (PSA screening reduced cancer-related 240 mortality by 4 men for every 1000 men, after 14 years of follow-up) [35].

241 In breast cancer, the ANN did not reach good performances. The small variability of incidence 242 data from 1990 to 2050, together with the high multifactoriality of this tumor, may partially explain 243 the less good performance of our ANN in this disease (as evident from the regression curves in Figure 244 S3). This evidence suggests that the number of new cases does not strictly follow the trends registered 245 for age and obesity in USA (i.e. the peak from 1995 to 2002 in cancer incidence in a time-interval 246 characterized by the reduction of both risk factors) and underlines the necessity of identifying more 247 effective input variables beyond the most commonly recognized risk factors.

248 As for colorectal cancer, the drop of the incidence rates before 2000 should be explained by the 249 changes in risk factors and the introduction of screening (Fecal Occult Blood Testing (FOBT) and 250 endoscopy) [36]. The prevalence results distinct between men and women due to a series of 251 underlying different mechanisms that include estrogen exposure, menopausal status, insulin 252 resistance, chronic inflammation and steroid hormones [37, 38].

253 Lung cancer is among the most deadly cancers for both men and women [39]. Reducing its 254 incidence represents a major goal for cancer researchers, and both the results of these enforces and 255 the worldwide prevention campaigns to decrease tobacco consumption find a mirror in Figure 4A 256 showing the falling incidence of lung cancer. This progressive reduction would be even more rapid 257 as an effect of the global action towards the 2040 tobacco-free world goal [40]. As for the gender 258 differences (Figure 4B, 4C), they reflect the historical attitudes in tobacco use, with women starting 259 to smoke in large numbers later and at older ages than men.

260 Our study presents several limitations. As other prediction systems, ANN algorithms are 261 affected by errors and biases compared to real data. However, ANNs provide for training, 262 performance and validation phases that may partially reduce system biases and increase the accuracy 263 of predictions.

- 5. Conclusions
- 265 266

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267 This up-to-date prediction of cancer burden in the United States could be a crucial resource for 268 planning and evaluation of cancer-control programs. Urgent global actions towards a dramatic 269 reduction of cancer-related risk-factors are actually needed and will accelerate the drop of incidences and the route to cancer eradication in future years.

271

272 Supplementary material:

273 Figure S1. The flow of the Artificial Neural Network (ANN) algorithm employed in this study.

274 Figure S2. Performance of Train and Validation phases for prostate cancer by ethnicity. Data were

275 scaled into the range used by the input neurons in the neural network. In this case the range is -1 to 276 1 (A=all races; B=White; C=Black; D=Hispanic; E=Asian/Pacific Islander; F=American Indian/Alaska

277 Native).

278 Figure S3.Performance of Train and Validation phases for breast cancer. Data were scaled into the 279 range used by the input neurons in the neural network. In this case the range is -1 to 1. Mean squared

280 normalized errors for the Train and Validation sets are respectively 0.27882 and 0.14008.

270

- Figure S4. Performance of Train and Validation phases for breast cancer. Data were scaled into the range used by the input neurons in the neural network. In this case the range is -1 to 1 (A=total population; B=males; C=females).
- Figure S5. Performance of Train and Validation phases for lung cancer. Data were scaled into the range used by the input neurons in the neural network. In this case the range is -1 to 1 (A=total population; B=males; C=females).
- 287
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 NB; writing (final editing): LC, ALB, AC, RM (Rodolfo Montironi).

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- 296 Conflicts of Interest
- 297 The authors declare to have no conflicts of interest.
- 299 Abbreviations
- 300 ANN Artificial Neural Network
- 301 BMI Body Mass Index
- 302 FDA Food and Drug Administration
- 303 FOBT Fecal Occult Blood Testing
- 304
 LM
 Learning Momentum
- 305 LR Learning Rate
- 306MLPMultilayered Perceptrons
- 307 MSE Mean Square Error
- 308 PSA Prostate-Specific Antigen
- 309 USPSTF US Preventive Services Task Force
- 310

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