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note finali coverage

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1 Article

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

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

34 According to our predictions, the rapid decreasing trend of prostate cancer incidence started in 2010  
35 will continue until 2018/2019 and then it will slow down and reach a plateau after 2050, with several  
36 differences among different ethnicities. The incidence of breast cancer will reach a plateau in 2030,  
37 while colorectal cancer incidence will reach a minimum value of 30/100.000 in 2025, followed by a  
38 plateau in 2030 in men and in 2050 in women. As for lung cancer, the incidence will decrease from  
39 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.

44 **Keywords:** Artificial Neural Network; Breast cancer; Colorectal cancer; Future tumor burden; Lung cancer;  
45 Prostate Cancer.

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## 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

### 79 2.1 Data sets

80 USA population and USA life expectancy data derived from Gapminder ([www.gapminder.org](http://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.

### 88 2.2 Implementation of Artificial Neural Networks

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

96 Age is a commonly known factor associated with the risk of breast cancer [23]. It is estimated  
97 that females who survive till 85 years will present a lifetime rate of approximately 11% of developing  
98 breast cancer [23]. Similarly, obesity is associated with an increased risk of both premenopausal [24]  
99 and postmenopausal breast cancer [25], being also associated with worse cancer-related survival in

100 all breast cancer subtypes. To predict the incidence of breast cancer in USA, our ANN was based on  
101 (1) demographic trend, (2) life expectancy data and (3) obesity. Data from 1992 to 2013 were used for  
102 training and validation and data from 2014 to 2050 were predicted. As for prostate cancer, here we  
103 considered total population as an input variable.

104 The risk of developing colorectal cancer increases with age, with more than 90% of cases  
105 occurred in patients who are 50 years old or older [26]. It has been estimated that 29.5% of colorectal  
106 cancers can be attributable to a Body Mass Index (BMI)>22.5 [27], with an incidence that results  
107 different between men and women [28]. To predict the future incidence of colorectal cancer in USA,  
108 we included (1) demographic trend, (2) life expectancy data and (3) obesity as inputs of the ANN  
109 algorithm. Data from 1975 to 2013 were used for training and validation and data from 2014 to 2050  
110 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.

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### 138 **3. Results**

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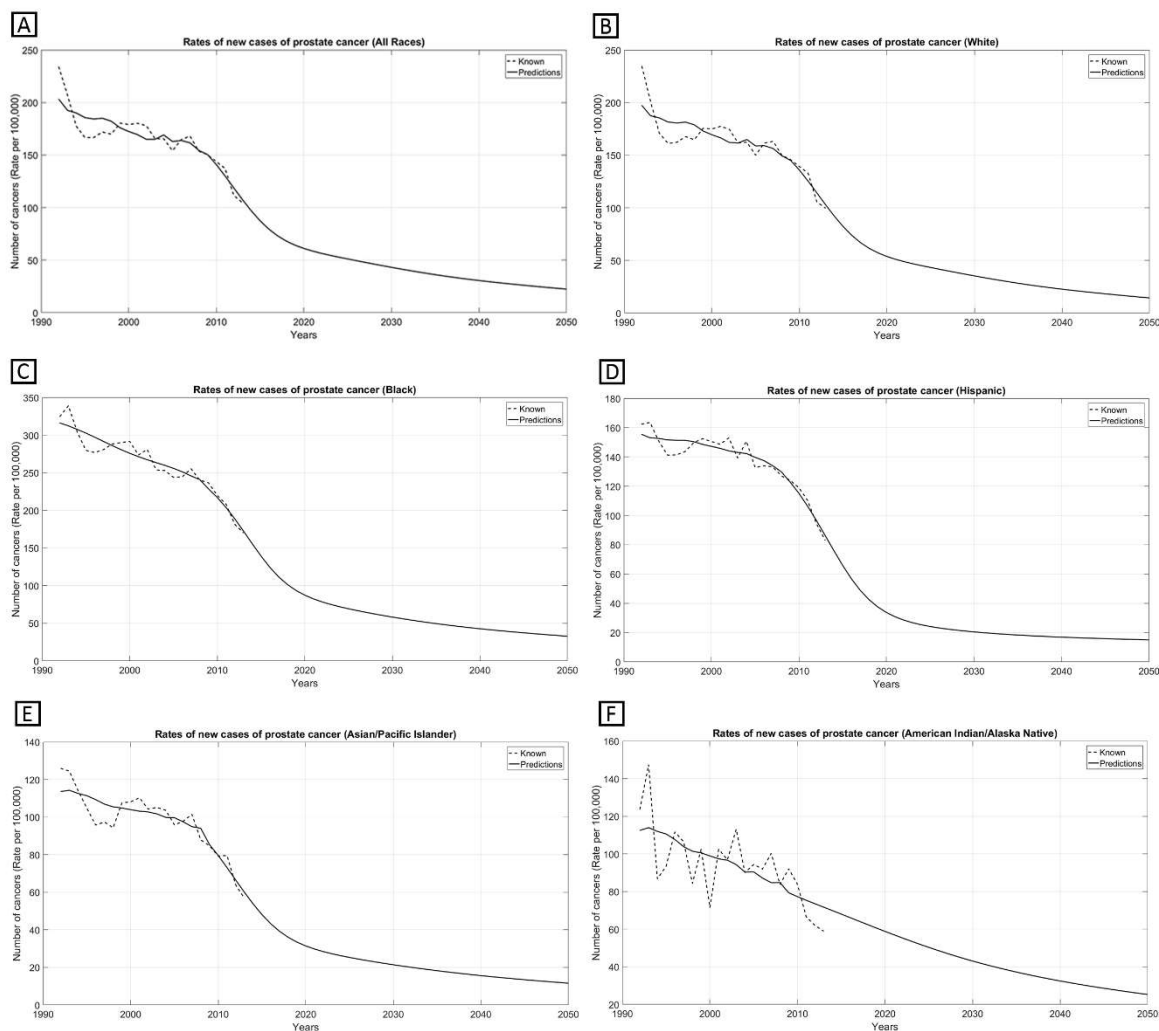
#### 140 *3.1 Prostate cancer*

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 than  
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

151 Alaska native are characterized by a lower incidence (Figure 1E, 1F). Only for American  
 152 Indian/Alaska Native Races the decreasing trend is almost steady (Figure 1F).

153

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



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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.

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### 3.2 Breast cancer

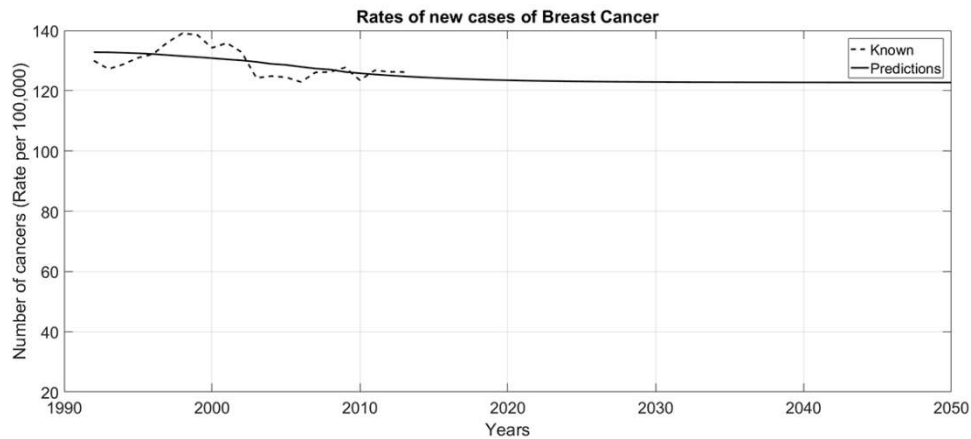
163

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

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172 **Figure 2.** Trend and predicted new cases of breast cancer. Our calculations are based on  
 173 population, life expectancy and obesity data for female.

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### 3.3 Colorectal cancer

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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).

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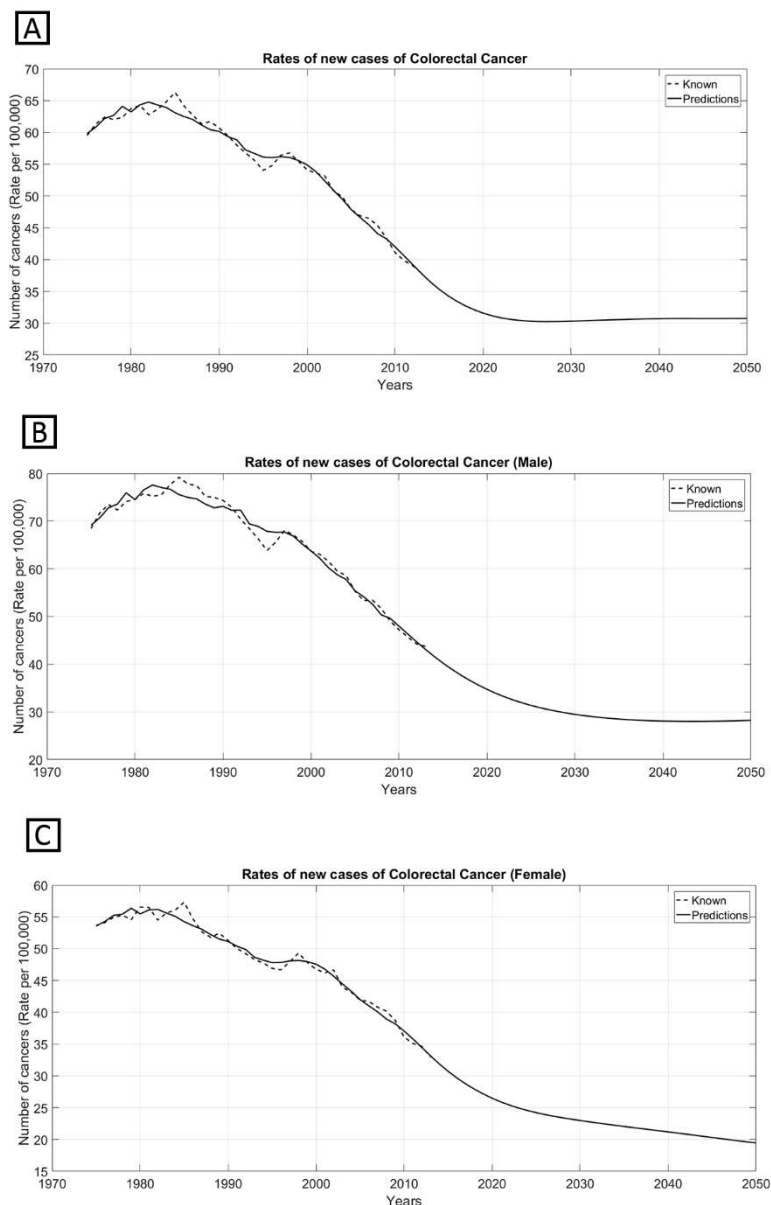
Due to the influence of gender on colorectal cancer incidence [33], we further predicted the incidence in males (Figure 3B) and females (Figure 3C). We found that the incidence was maximum for men in 1985 (79/100.000) and for women in 1985 (57/100.000), respectively (Figure 3B, 3C). Interestingly, we 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).

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**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 and females.



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### 3.4 Lung cancer

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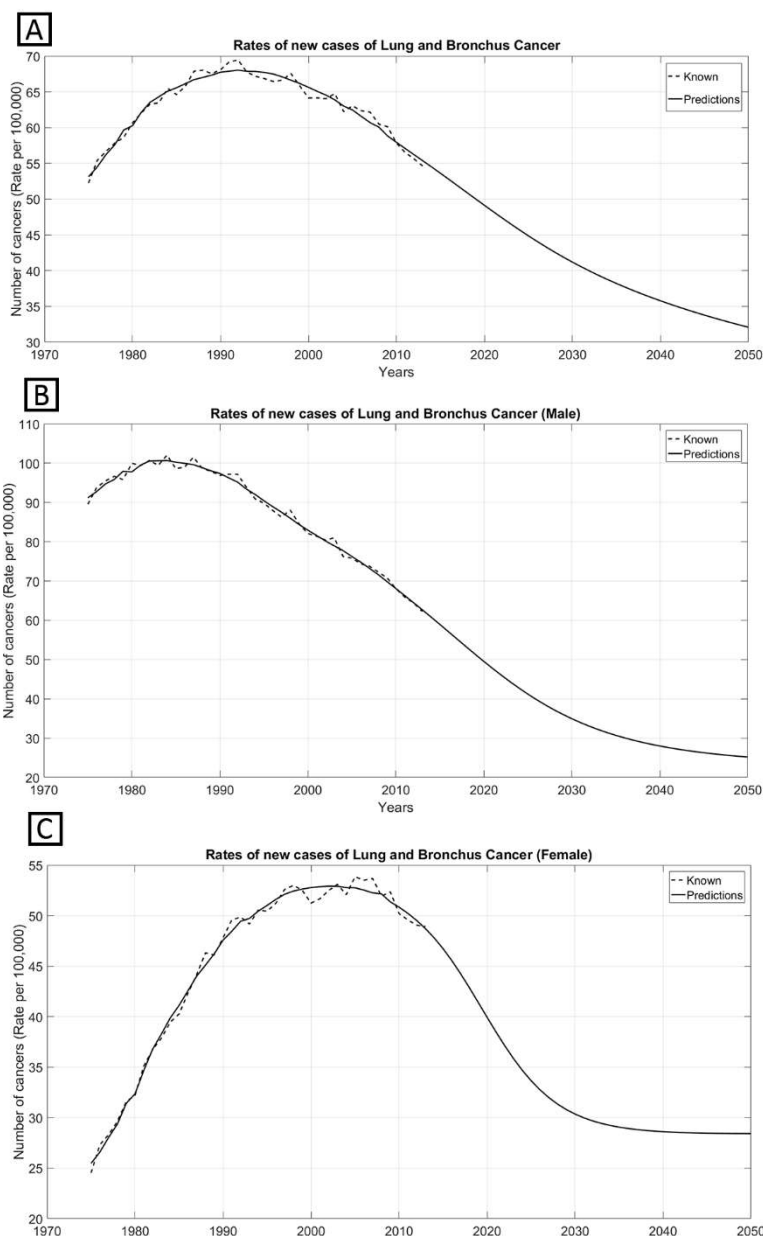
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The incidence of lung cancer has progressively increased from 1970s (53 cases/100.000 habitants), registering its maximum in 1992, characterized by 69/100.000 (Figure 4A). From 1990s, the downward trend in the smoking attitude has led to a gradually 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 and females.



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### 3.5 Regression Analysis

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

## 4. Discussion

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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.

## 264 5. Conclusions

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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  
270 and the route to cancer eradication in future years.

### 271 Supplementary material:

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

273 **Figure S2.** Performance of Train and Validation phases for prostate cancer by ethnicity. Data were  
274 scaled into the range used by the input neurons in the neural network. In this case the range is -1 to  
275 1 (A=all races; B=White; C=Black; D=Hispanic; E=Asian/Pacific Islander; F=American Indian/Alaska  
276 Native).

277 **Figure S3.** Performance of Train and Validation phases for breast cancer. Data were scaled into the  
278 range used by the input neurons in the neural network. In this case the range is -1 to 1. Mean squared  
279 normalized errors for the Train and Validation sets are respectively 0.27882 and 0.14008.  
280

281 **Figure S4.** Performance of Train and Validation phases for breast cancer. Data were scaled into the  
 282 range used by the input neurons in the neural network. In this case the range is -1 to 1 (A=total  
 283 population; B=males; C=females).

284 **Figure S5.** Performance of Train and Validation phases for lung cancer. Data were scaled into the  
 285 range used by the input neurons in the neural network. In this case the range is -1 to 1 (A=total  
 286 population; B=males; C=females).

287  
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289 **Author contribution:** conceptualization: MS and FT; methodology: FP, MG, MMA; data  
 290 curation: FP, MS, RM (Roberta Mazzucchelli), RC; writing (original draft preparation): FT, MS, FP,  
 291 NB; writing (final editing): LC, ALB, AC, RM (Rodolfo Montironi).

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#### Conflicts of Interest

297 The authors declare to have no conflicts of interest.

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#### 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
306	MLP	Multilayered Perceptrons
307	MSE	Mean Square Error
308	PSA	Prostate-Specific Antigen
309	USPSTF	US Preventive Services Task Force

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