

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

**Mediating role of lifestyle behaviors in the association between education and cancer: results from the European Prospective Investigation into Cancer and Nutrition**

**This is the author's manuscript**

*Original Citation:*

*Availability:*

This version is available <http://hdl.handle.net/2318/1880403> since 2023-01-03T14:55:13Z

*Published version:*

DOI:10.1158/1055-9965.EPI-22-0777

*Terms of use:*

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

**Title: Mediating role of lifestyle behaviours in the association between education and cancer: results from the European Prospective Investigation into Cancer and Nutrition**

**Running title: Lifestyle behaviours mediating education and cancer risk**

Alessandra Macciotta<sup>1\*</sup>, Alberto Catalano<sup>1</sup>, Maria Teresa Giraudo<sup>2</sup>, Elisabete Weiderpass<sup>3</sup>, Pietro Ferrari<sup>3</sup>, Heinz Freisling<sup>3</sup>, Sandra M. Colorado-Yohar<sup>4,5,6</sup>, Carmen Santiuste<sup>4,5</sup>, Pilar Amiano<sup>7,5</sup>, Alicia K Heath<sup>8</sup>, Heather A Ward<sup>8</sup>, Sofia Christakoudi<sup>8,9</sup>, Paolo Vineis<sup>8</sup>, Deependra Singh<sup>3</sup>, Salvatore Vaccarella<sup>3</sup>, Matthias B Schulze<sup>10,11</sup>, Anouk E Hiensch<sup>12</sup>, Evelyn M Monninkhof<sup>12</sup>, Verena Katzke<sup>13</sup>, Rudolf Kaaks<sup>13</sup>, Rosario Tumino<sup>14</sup>, Fulvio Lazzarato<sup>15</sup>, Lorenzo Milani<sup>16</sup>, Antonio Agudo<sup>17</sup>, Christina C Dahm<sup>18</sup>, Laura Baglietto<sup>19,20</sup>, Vittorio Perduca<sup>21,20</sup>, Gianluca Severi<sup>20,22</sup>, Sara Grioni<sup>23</sup>, Salvatore Panico<sup>24</sup>, Eva Ardanaz<sup>25,5</sup>, Kristin B Borch<sup>26</sup>, Faith O Benebo<sup>26</sup>, Tonje Braaten<sup>26</sup>, Maria-Jose Sánchez<sup>27,28,5,29</sup>, Claudia Giachino<sup>1</sup>, Carlotta Sacerdote<sup>15,§</sup>, Fulvio Ricceri<sup>1,30,§</sup>

<sup>1</sup>Department of Clinical and Biological Sciences, University of Turin, Italy

<sup>2</sup>Department of Mathematics “G. Peano”, University of Turin, Italy

<sup>3</sup>International Agency for Cancer Research (IARC-WHO), Lyon, France

<sup>4</sup>Department of Epidemiology, Murcia Regional Health Council, IMIB-Arrixaca, Murcia, Spain.

<sup>5</sup>CIBER Epidemiología y Salud Pública (CIBERESP), Madrid, Spain.

<sup>6</sup>Research Group on Demography and Health, National Faculty of Public Health, University of Antioquia, Medellín, Colombia

<sup>7</sup>Ministry of Health of the Basque Government, Sub Directorate for Public Health and Addictions of Gipuzkoa, Biodonostia Health Research Institute, San Sebastian, Spain

<sup>8</sup>Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, UK

<sup>9</sup>MRC Centre for Transplantation, King's College London, Great Maze Pond, London, UK

<sup>10</sup>Dept. of Molecular Epidemiology, German Institute of Human Nutrition, Nuthetal, Germany

<sup>11</sup>Institute of Nutritional Science, University of Potsdam, Potsdam, Germany

<sup>12</sup>Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, The Netherlands

<sup>13</sup>Division of Cancer Epidemiology, German Cancer Research Center (DKFZ), Heidelberg, Germany

<sup>14</sup>Hyblean Association for Epidemiological Research, AIRE-ONLUS, Ragusa, Italy

<sup>15</sup>Unit of Cancer Epidemiology, “Città della salute e della scienza” University-Hospital, Turin, Italy

<sup>16</sup>Department of Medical Science, University of Turin, Italy

<sup>17</sup>Unit of Nutrition and Cancer, Catalan Institute of Oncology - ICO, L'Hospitalet de Llobregat, Spain

<sup>18</sup>Department of Public Health, Aarhus University, Denmark

<sup>19</sup>Department of Clinical and Experimental Medicine, University of Pisa, Italy

<sup>20</sup>Paris-Saclay University, UVSQ, Inserm, Gustave Roussy, "Exposome and Heredity" team, CESP, F-94805, Villejuif, France

<sup>21</sup>Laboratoire MAP5 (UMR CNRS 8145), Université de Paris, F-75006 Paris, France

<sup>22</sup>Department of Statistics, Computer Science and Applications "G. Parenti" (DISIA), University of Florence, Italy

<sup>23</sup>Epidemiology and Prevention Unit, Fondazione IRCCS Istituto Nazionale dei Tumori di Milano, Italy

<sup>24</sup>Dipartimento Di Medicina Clinica E Chirurgia Federico II University, Naples, Italy

<sup>25</sup>Navarre Public Health Institute, Pamplona, Spain

<sup>26</sup>Department of Community Medicine, UiT, the Arctic University of Norway

<sup>27</sup>Escuela Andaluza de Salud Pública (EASP), Granada, Spain

<sup>28</sup>Instituto de Investigación Biosanitaria ibs.GRANADA, Spain

<sup>29</sup>Department of Preventive Medicine and Public Health, University of Granada, Spain.

<sup>30</sup>Unit of Epidemiology, Regional Health Service ASL TO3, Grugliasco (TO), Italy

§Joint last authors

\* Corresponding author:

Alessandra Macciotta

Department of Clinical and Biological Sciences, University of Turin

Regione Gonzole 10, 10043 Orbassano (TO), Italy

e-mail: [alessandra.macciotta@unito.it](mailto:alessandra.macciotta@unito.it)

The authors declare no potential conflicts of interest.

## **Abstract**

**Background:** Many studies have shown that socioeconomic position (SEP) is associated with the incidence of malignant tumors at different sites. This study aims to estimate the association between educational level (as proxy for SEP) and cancer incidence and to understand if the observed associations might be partially explained by lifestyle behaviors.

**Methods:** The analyses were performed on data from the European Prospective Investigation into Cancer and Nutrition (EPIC) study, globally and by sex. We used Cox proportional hazards models together with mediation analysis to disentangle the total effect (TE) of educational level (measured through the Relative Index of Inequality (RII)) on cancer incidence into pure direct (PDE) and total indirect (TIE) effect, unexplained and explained by mediators, respectively. PDE and TIE were then combined to compute the proportions mediated (PM).

**Results:** After an average of 14 years of follow-up, 52,422 malignant tumors were ascertained. Low educated participants showed higher risk of developing stomach, lung, kidney (in women), and bladder (in men) cancers, and, conversely, lower risk of melanoma and breast cancer (in post-menopausal women), when compared to more educated participants. Mediation analyses showed that portions of the total effect of RII on cancer could be explained by site-specific related lifestyle behaviors for stomach, lung, and breast (in women).

**Conclusions:** Cancer incidence in Europe is determined at least in part by a socioeconomically stratified distribution of risk factors.

**Impact:** These observational findings support policies to reduce cancer occurrence by altering mediators, such as lifestyle behaviors, particularly focusing on underprivileged strata of the population.

## Introduction

In 1997 Krieger et al [1] defined the socioeconomic position (SEP) as an “aggregate concept that includes both resource-based and prestige-based measures, as linked to both childhood and adult social class position”. In order to measure this phenomenon, different indicators [2] have been considered in epidemiological research. Some examples are one’s own and parents’ income, educational level, and occupation, as well as housing tenure and conditions. Even if those indicators are often correlated and used interchangeably, they measure different stages of SEP during life course. Above all, education may play a crucial role in epidemiological research because, being related to parents’ and personal socioeconomic indicators, it can capture both childhood and adult SEP [3].

Differences in health outcomes by SEP have been reported consistently [4] for several non-communicable diseases. It has been estimated that low SEP may have an impact in terms of reducing life expectancy which is comparable to the effects on health caused by best known risk factors, such as smoking or sedentary lifestyles [5].

Special attention should be paid to the association between SEP and cancer at different sites: indeed, much evidence has been obtained that SEP is related to cancer incidence [6], though with different gradients and trends. It has been shown that in high income countries people with a low SEP are more at risk for cancers of Upper Aero-Digestive Tract, kidney, liver, pancreas, bladder, and cervix, while have lower incidence of melanoma and lymphoma and of thyroid, brain, testicular, colorectal and breast cancers [7-10]. For lung tumors, disparities have been observed between men and women: in Mediterranean countries, such as Italy, Spain, and Slovenia, women with a low SEP were found to be at a lower risk of developing cancer at this site, while in northern countries both women and men with a low SEP showed similar higher risks when compared to people with a better SEP [11].

Cancer incidence occurs after a chain of events caused by different factors spread over time. Based on their position on the causal chain, those factors are defined as proximal or distal. Proximal factors cause the disease directly, while distal determinants, positioned further back in the chain, cause it through different pathways [12].

SEP does not act directly on carcinogenesis, but may induce lifestyle behaviors, biological factors, and material circumstances [13] implicated in the causal chain of cancer. Furthermore, SEP may influence different access to health care services: people with a high SEP undergo more check-ups

and visits and the higher incidence of cancer at some sites may be explained by over or earlier diagnosis [14].

The aim of this investigation is, firstly, to estimate the associations between educational level, as a proxy for SEP, and cancer at different sites and, secondly, to disentangle these effects considering site-specific pathways through factors related to lifestyle behaviors.

## **Materials and Methods**

### *Study population*

The European Prospective Investigation into Cancer and Nutrition (EPIC) cohort consists of about 500,000 volunteers, enrolled between 1992 and 1999 in ten European Countries, for whom data about lifestyle behaviors, indicators for SEP, and cancer incidence during the follow-up were available; details are described elsewhere [15]. For this study, participants with detailed information for the considered variables and belonging to nine EPIC studies have been included.

### *Exposure, mediators, and outcome*

The exposure, SEP, was assessed through a standardized index, the Relative Index of Inequality (RII), that takes into account the educational level (as a proxy for SEP and expressed as highest school level achieved) and allows study participants from different birth cohorts and Countries to be compared. The RII was assigned by ranking reported educational levels according to the proportion of participants within relevant strata for each Country, by 10-year age groups and by sex [16]. Three categories were then created according to the tertiles of the RII's distribution for the study population: first, second, and third tertiles correspond to high, medium, and low educational level, respectively.

Effects of RII on cancer incidence were evaluated considering the most common sites (those with approximately one thousand cases or more in the EPIC cohort) separately: stomach, colorectum, lung, melanoma, breast (only in post, peri, or surgical menopausal women), uterus, ovary, prostate, kidney, bladder, and lymphoma. Participants were followed from the date of recruitment until the date of a primary cancer diagnosis, death, or last follow-up, whichever occurred first.

For cancer sites for which a statistically significant association with RII was found, putative site-specific mediators were sought in the literature to identify factors related to lifestyle behaviors that are associated with both educational level and site-specific cancer incidence.

### *Statistical analysis*

Overall and sex-specific Cox proportional hazards regression models were used to estimate possible socioeconomic inequalities in relation to the incidence of site-specific tumors. All models were adjusted for age and country and also for sex in the first case and the results were expressed as hazard ratios (HRs) and 95% confidence intervals (CIs).

For mediation analyses, a novel approach [17], based on the counterfactual technique introduced by VanderWeele, was applied. It is an extension to survival outcomes of a weighted method, which allows inclusion of multiple non-independent mediators. It enables to disentangle the total effect (TE) of an exposure on an outcome into total indirect (TIE) and pure direct (PDE) effect. In this context, TE expresses the effect of the exposure (RII) on the outcome of interest (site-specific cancer occurrence); TIE reveals which part of TE passes through the mediators (site-specific lifestyle factors); PDE expresses how much of TE cannot be explained by the mediators included in the model. The Directed Acyclic Graph (DAG) shown in Figure 1 sketches the mediation pathways mentioned above.

Firstly, standard analyses to evaluate exposure-mediators and mediators-outcome associations were carried out. For exposure-mediators associations, linear, logistic, and multinomial regressions were performed depending on each mediator's distribution; Cox regression models were used to estimate mediators-outcome associations.

The sequential temporality of the variables involved in the mediation pathway must be plausible and was guaranteed by the fact that individual measurements of hypothesized mediating variables dated back to the recruitment in the cohort, in between the achievement of educational degree and incidence of cancer. Furthermore, to identify and estimate causal effects, all potential confounders of exposure-outcome, mediators-outcome and exposure-mediator associations should be included in the model.

Secondly, TIE, PDE, and TE were estimated through the weighted approach, approximately once per year along the observed survival times. Indeed, the marginal hazard function could not always satisfy the proportionality assumption and hence the effects may vary over time.

Cox regression models and mediation analyses were performed both on the overall sample and separately in men and women. CIs were constructed as 95% bootstrap CIs using the percentile method.



Finally, when in the same direction, TIE and PDE were then combined to measure how much of TE was explained by the considered mediators. The proportions mediated (PM) were computed through the following formula, proposed by VanderWeele and Vansteelandt:

$$((HR^{PDE} * (HR^{TIE} - 1)) / (HR^{PDE} * HR^{TIE} - 1)) [18].$$

The analyses were conducted using Stata (StataSE 13) and R (version R 3.6.3) and p-value < 0.05 was considered statistically significant.

### **Data availability**

Raw data cannot be made freely available due to restrictions imposed by the Ethical Committees which do not allow open/public sharing of data on individuals. However, aggregated data are available upon request. Requests should be sent to the corresponding author.

### **Results**

#### *Population description*

Demographic, cancer incidence, and lifestyle behavior features according to RII tertiles distribution in the overall population are described in Table 1 where means (standard deviations) and frequencies (percentages) are shown. In each group the mean age at recruitment was about 50 years and there was a majority of females (approximately 70%). The incidence of stomach, colorectal, lung, kidney, bladder cancers, and lymphoma was higher in the third tertile of RII when compared to the first and second tertile.

Poor lifestyle habits, such as smoking and low adherence to the Mediterranean diet, were more prevalent among people belonging to the lowest educational level (third RII tertile): 25.8% of the individuals in the third tertile of RII were smokers versus 19.2% in the first one, while almost half of the study participants in the first tertile reported following a Mediterranean diet (got at least 4 for the Trichopoulou diet score [19]) compared to 43.9% of those in the third one. Similar trends were observed for physical conditions like obesity (16.7% in the third tertile of RII versus 8.4% in the first one) and hypertension (24.5% versus 17.6%).

Conversely, study participants belonging to the first RII tertile consumed more alcohol and spent more hours in recreational activities than those with a lower educational level (third RII tertile).

Supplementary Table S1, similarly to Table 1, shows demographic features, cancer incidence and the statistics on lifestyle behaviors in men. It displays the incidence of prostate cancer, which appears to be the most common tumor in the male cohort, with an incidence of about 5% in all the three RII groups.

Further differences, according to RII, were found in breast cancer incidence in the female cohort (Supplementary Table S2): 4.3% of women with a low educational level (in the third RII tertile) developed a breast tumor during the follow-up, compared to 5% of more educated women (both in the first and in the second tertile of RII). In terms of reproductive history, the majority (63.0%) of women in the third tertile had their first full term pregnancy before turning 26 (versus 36.2% in the first tertile), while the percentage of nulliparous women were higher in the first tertile (21.0%) when compared to that in the third one (11.6%).

Supplementary Table S3 shows the variables distribution according to both sex and country.

#### *Cox models - Associations between educational level and cancer risk*

Table 2 shows the results for the overall sample (adjusted for sex, age, and Country), and for the sample stratified by sex (and adjusted for age and Country).

Study participants in the third tertile of RII (the lowest educational level) expressed overall higher risks for stomach (HR=1.50; 95%CI=[1.27-1.78]) and lung (HR=1.93; 95%CI=[1.77-2.10]) cancers, together with a lower risk for melanoma (HR=0.79; 95%CI=[0.74-0.86]) when compared to study participants in the first tertile (the highest educational level). For stomach, and lung cancers and for melanoma, sex-specific estimates were consistent with overall HRs.

Further sex-specific associations were found for breast and prostate cancers, for which lower educational level was associated with a reduced risk (breast cancer in women HR=0.87; 95%CI=[0.84-0.90] and prostate cancer HR=0.88; 95%CI=[0.83-0.93] for third versus first tertile of RII). In the opposite direction, lower educational level was associated with an increased risk for kidney and bladder cancer (kidney in women HR=1.41; 95%CI=[1.12-1.78] and bladder in men HR=1.19; 95%CI=[1.03-1.39]).

#### *Mediation analyses*

Based on the Cox models results, an in-depth literature review was performed to find putative mediating factors for the statistically significant associations between RII and site-specific cancers.

Table 3 shows the mediating factors, as well as details on the distribution of the variables considered for the analyses, that were identified in the literature and available in the EPIC cohort.

A recent systematic review [20] and an International Agency for Research on Cancer (IARC) Scientific Publication [21] helped to identify lifestyle related and reproductive factors influenced by SEP. Then, further investigations allowed to find out which of those factors could be associated with the incidence of stomach [22], melanoma [23], lung [24], kidney [25], bladder [26], and breast [27,28] cancers. No putative mediators were found for prostate cancer.

Supplementary Table S4 and Supplementary Table S5 show the results of models devised to investigate the hypotheses to be fulfilled to perform mediation analysis. Table S4 shows the associations between RII and each mediator, while Table S5 shows the associations between each mediator and site-specific cancer incidence. A statistically significant association ( $p < 0.01$ ) was found between RII and all the mediators considered (alcohol consumption, physical recreational activities, Body Mass Index (BMI), smoking, hypertension, adherence to the Mediterranean diet, reproductive history, and breastfeeding). Cox models confirmed the expected associations between each mediator and site-specific cancer incidence except for alcohol consumption and stomach cancer, and smoking status and breast cancer. Nevertheless, due to the evidence found in the literature [22,27], we decided to keep both of them for the mediation analyses.

Table 4 shows the estimates of TIE, PDE, and TE obtained in the mediation analyses and computed at the median of the follow-up time (11 years), for the second and third RII tertile (medium and low educational level) when compared to belonging to the first one (high educational level). Supplementary Figure S1 shows the effects computed over the entire follow-up. The total effect of belonging to the third tertile of RII if compared to belonging to the first one could be partially disentangled through the indirect effect of the site-specific lifestyle behaviors considered for stomach (overall TIE: HR=1.09; 95%CI=[1.06-1.12]; PDE: HR=1.42; 95%CI=[1.21-1.70]), lung (overall TIE: HR=1.23; 95%CI=[1.21-1.25]; PDE: HR=1.62; 95%CI=[1.49-1.76]), breast (women TIE: HR=0.95; 95%CI=[0.94-0.97]; PDE: HR=0.93; 95%CI=[0.88-0.98]), kidney (overall TIE: HR=1.13; 95%CI=[1.09-1.17]; PDE: HR=0.94; 95%CI=[0.78-1.11]), and bladder (overall TIE: HR=1.13; 95%CI=[1.11-1.15]; PDE: HR=1.09; 95%CI=[0.96-1.25]) cancers. No significant indirect effect in the path between RII and melanoma was observed, when considering the chosen possible mediators.

The proportions mediated [18] allow to quantify the amount of the TE of RII on the incidence of site-specific cancers that may operate through the mediators considered.

In details, 23% (13% in men and 39% in women) of the association of the lowest educational level (in the third RII tertile) on higher incidence of stomach cancer when compared to the first RII tertile could be explained by differences in smoking, alcohol intake, dietary habits, and BMI. For lung cancer, more than 30% of the higher risk could be explained by smoking habits, both in the overall cohort and separately in men and women. 40% of the reduced risk of developing breast cancer for less educated women compared to those with a higher educational level could be explained by differences in reproductive history, breast feeding, BMI, smoking and dietary habits (including alcohol), while 58% of the increased risk of developing kidney cancer could be explained by smoking habits, BMI, and hypertension. Finally, more than 60% of the increased risk of developing bladder cancer in men could be due to smoking.

## **Discussion**

The recent definition of cancer as “a disease of difference” [6] by the IARC fully highlights the complexity of the micro and macro levels involved in the development of tumors. Indeed, disparities exist on one hand in the molecular, cellular, and morphological pathways, and on the other hand in the incidence distribution. Educational level, as a proxy for SEP, is recognized to be associated with the occurrence of cancer at several sites [29]. Socioeconomic differences in cancer incidence have been observed in almost all European countries: France [30], Italy [31], Germany [32], United Kingdom [33], Ireland [34], Sweden [35], Iceland [36], and Lithuania [37].

Previous studies in the EPIC cohort had already suggested the existence of a significant association between educational level and cancer occurrence at some of the studied cancer sites, such as stomach and breast [7,38], as well as with all-cause mortality [39] and incidence of other chronic diseases [40,41].

In this large prospective European cohort, we found that men and women with a lower educational level (standardized by cohort, sex, and Country as measured through the RII) are at a higher risk of developing stomach, lung, kidney (in women), and bladder (in men) cancers, while, on the contrary, they appear to have lower risk for melanoma and for breast and prostate cancer, when compared to more educated individuals. We found no association between RII and colorectal, uterus, ovarian cancers, and lymphomas.

To understand if some portions of the effect of RII on cancer risk could be explained by lifestyle related and reproductive factors, we implemented a mediation analysis, considering as mediators the available measured behaviors known to be involved in the developmental pathway of each cancer site [20-28]. The combination of indirect effect (measured through TIE) and direct effect (measured through PDE) into PM contributed to identify how much of the association between education and cancer is related to a different distribution of behavioral factors by educational level. The complementary to 100% expresses how much of the association between educational level and cancer is due to an indirect effect other than to the mediators considered.

In details, we observed that for stomach cancer in both men and women the effect of educational level was partially mediated by the uneven distribution of lifestyle risk factors such as smoking status, alcohol consumption, adherence to Mediterranean diet, and BMI, as expected [42]. However, the direct component remained high and this may be due to a different distribution of *Helicobacter pylori* infection, of environmental exposures (e.g. arsenic) [43], and of biomarkers (e.g.: microsatellite instability) that are involved in molecular pathways of gastric carcinogenesis [44].

Considering lung cancer, smoking is known to be a strong mediator of the analyzed relationship [45] and our data confirmed this previous result. Smoking acted as a particularly relevant mediator also in the relationship between RII and bladder cancer and this is coherent with the etiology of lung cancer [46]. Moreover, we observed that smoking, together with BMI and hypertension, strongly mediated the association between educational level and kidney cancer, especially in women, as has also been observed in a Norwegian cohort study [47].

The lower risk in less educated people for the incidence of melanoma, largely described in literature [8], was not observed to be mediated by smoking status and recreational physical activity. Investigating intermediate risk factors has seldom been performed in other studies and a possible hypothesis of other mediators is that people with higher SEP are more exposed to high intermittent sun exposure (because they might be more likely to go on holidays to sunny destinations), as found for Norwegian women [47]. However, due to unavailability of information on the topic in the EPIC study, we could not verify this possible mediating pathway. Furthermore, part of the observed effect of SEP on melanoma could be explained by over detection due to screening examinations, usually more common among highly educated women. Periodic screening visits may result in both early diagnosis and detection of clinically insignificant lesions [48].

The association between lower educational level and decreased risk of breast cancer was mediated by different distribution of smoking status, alcohol consumption, adherence to Mediterranean diet, BMI, breastfeeding, and age at first pregnancy. Post, peri or surgical menopausal women (i.e. middle aged or old women) recruited in the 90's mainly reported typical female conditions of the last century, in which smoking or drinking habits were more common among more educated women, as well as obesity. Moreover, this result is coherent with the literature where age at first pregnancy seemed to explain most of the SEP effect [49,50,51]. As for melanoma, a contribution of over diagnosis may partially explain the effect of SEP on the incidence of breast cancer, especially for *in situ* tumors [29].

As far as we know, our study is the first systematic analysis performed to understand the behavioral components of the association between educational level and cancer through a rigorous methodology, the mediation analysis based on counterfactual approach and weighted methods. Furthermore, temporal relationship pathways were guaranteed by the longitudinal design of the study: the exposure was a standardized proxy for early life SEP, mediators were measured at baseline and cancer incidence was observed during follow-up.

However, some limitations should also be considered. Firstly, information on several possible mediators were unavailable in this study: the inclusion of preclinical biomarkers could lead to a meet-in-the-middle approach, with the goal of strengthening the causal hypothesis [52]. These factors could increase the risk of cancer and further explain portions of the total effect of educational level on cancer. Nevertheless, the portion of effect that unknown or unmeasured missing mediators could explain remains included in the direct effect and should not bias the analyses. Secondly, mediators were measured at a single point in time at recruitment and not updated during the follow-up; in addition, some of them were categorized according to cut-offs commonly adopted in the literature, which may have led to a loss of precision in the final estimates. Thirdly, the method applied did not allow to estimate the contribution of each single mediator, but only an overall intermediate effect. Therefore, further studies are needed to disentangle the separate effects of each mediator. Moreover, the absence of information regarding *access to healthcare services* and *tumor stage* did not allow to investigate the role of the first variable as a mediator and to stratify the analyses according to the latter. At last, the possible presence of unknown potential confounders of exposure-outcome, mediators-outcome and exposure-mediator associations did not allow to infer causality of the associations.

In conclusion, according to the cohort data on which the study was based, we found that cancer incidence in Europe is determined at least in part by a socioeconomically stratified distribution of risk factors. Notably, since most of these risk factors are preventable, our findings support evidence in favor of policies to reduce cancer occurrence by altering mediators, such as lifestyle behaviors, particularly focusing on unprivileged strata of the population. Furthermore, once again, our results highlighted the association between educational level and health outcomes, suggesting that schools may have an important role in reducing inequalities and promoting health by developing health literacy [53].

## **Acknowledgments**

We would like to thank the center for High-Performance Computing for Artificial Intelligence (HCP4AI) at the University of Turin. The coordination of EPIC is financially supported by the International Agency for Research on Cancer (IARC) and also by the Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, which has additional infrastructure support provided by the NIHR Imperial Biomedical Research Centre (BRC). The national cohorts are supported by: Danish Cancer Society (Denmark); Ligue Contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Éducation Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid, German Cancer Research Center (DKFZ), German Institute of Human Nutrition Potsdam-Rehbruecke (DIfE), Federal Ministry of Education and Research (BMBF) (Germany); Associazione Italiana per la Ricerca sul Cancro (AIRC), Compagnia di San Paolo, and National Research Council (Italy); Dutch Ministry of Public Health, Welfare and Sports (VWS), Netherlands Cancer Registry (NKR), LK Research Funds, Dutch Prevention Funds, Dutch ZON (Zorg Onderzoek Nederland), World Cancer Research Fund (WCRF), Statistics Netherlands (The Netherlands); Health Research Fund (FIS), Instituto de Salud Carlos III (ISCIII), Regional Governments of Andalucía, Asturias, the Basque Country, Murcia, and Navarra, and the Catalan Institute of Oncology (ICO) (Spain); Swedish Cancer Society, Swedish Research Council, and County Councils of Skåne and Västerbotten (Sweden); Cancer Research UK (14136 to EPIC-Norfolk; C8221/A29017 to EPIC-Oxford), Medical Research Council (1000143 to EPIC-Norfolk; MR/M012190/1 to EPIC-Oxford) (United Kingdom).

## **Disclaimer**

Where authors are identified as personnel of the International Agency for Research on Cancer / World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer / World Health Organization.



## References

1. Krieger N, Williams DR, Moss NE. Measuring social class in US public health research: concepts, methodologies, and guidelines. *Annu Rev Public Health*. 1997;18:341-378.
2. d'Errico A, Ricceri F, Stringhini S, Carmeli C, Kivimaki M, Bartley M, *et al*. Socioeconomic indicators in epidemiologic research: A practical example from the LIFEPAATH study. *PLoS One*. 2017;12(5):e0178071. Published 2017 May 30.
3. Galobardes B, Shaw M, Lawlor DA, Lynch JW, Davey Smith G. Indicators of socioeconomic position (part 1). *J Epidemiol Community Health*. 2006;60(1):7-12.
4. Mackenbach JP, Kunst AE. Measuring the magnitude of socio-economic inequalities in health: an overview of available measures illustrated with two examples from Europe. *Soc Sci Med*. 1997;44(6):757-771.
5. Stringhini S, Carmeli C, Jokela M, Avendaño M, Muennig P, Guida F, *et al*. Socioeconomic status and the 25 × 25 risk factors as determinants of premature mortality: a multicohort study and meta-analysis of 1·7 million men and women [published correction appears in *Lancet*. 2017 Mar 25;389(10075):1194] [published correction appears in *Lancet*. 2017 Mar 25;389(10075):1194]. *Lancet*. 2017;389(10075):1229-1237.
6. Vaccarella S, Lortet-Tieulent J, Saracci R, Conway DI, Straif K, Wild CP. Reducing social inequalities in cancer: evidence and priorities for research. Lyon (FR): International Agency for Research on Cancer; 2019. (IARC Scientific Publications, No. 168.)
7. Nagel G, Linseisen J, Boshuizen HC, Pera G, Del Giudice G, Westert GP, *et al*. Socioeconomic position and the risk of gastric and oesophageal cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC-EURGAST). *Int J Epidemiol*. 2007;36(1):66-76.
8. Hermann S, Rohrmann S, Linseisen J, Nieters A, Khan A, Gallo V, *et al*. Level of education and the risk of lymphoma in the European prospective investigation into cancer and nutrition. *J Cancer Res Clin Oncol*. 2010;136(1):71-77.
9. Leufkens AM, Van Duijnhoven FJ, Boshuizen HC, Siersema PD, Kunst AE, Mouw T, *et al*. Educational level and risk of colorectal cancer in EPIC with specific reference to tumor location. *Int J Cancer*. 2012;130(3):622-630.
10. Cirera L, Huerta JM, Chirlaque MD, Overvad K, Lindström M, Regnér S, *et al*. Socioeconomic Effect of Education on Pancreatic Cancer Risk in Western Europe: An Update on the EPIC Cohorts Study. *Cancer Epidemiol Biomarkers Prev*. 2019;28(6):1089-1092.
11. Tanoue LT. Women and Lung Cancer. *Clin Chest Med*. 2021;42(3):467-482.

12. Guilbert JJ. The world health report 2002 - reducing risks, promoting healthy life. Educ Health (Abingdon). 2003 Jul;16(2):230.
13. Solar O, Irwin A. A conceptual framework for action on the social determinants of health. Social Determinants of Health Discussion Paper 2 (Policy and Practice).
14. Srivastava S, Koay EJ, Borowsky AD, De Marzo AM, Ghosh S, Wagner PD, *et al.* Cancer overdiagnosis: a biological challenge and clinical dilemma. *Nat Rev Cancer*. 2019;19(6):349-358.
15. Riboli E, Kaaks R. The EPIC Project: rationale and study design. European Prospective Investigation into Cancer and Nutrition. *Int J Epidemiol*. 1997;26 Suppl 1:S6-S14
16. Ricceri F, Sacerdote C, Giraudo MT, Fasanelli F, Lenzo G, Galli M, *et al.* The Association between Educational Level and Cardiovascular and Cerebrovascular Diseases within the EPICOR Study: New Evidence for an Old Inequality Problem. *PLoS One*. 2016;11(10):e0164130. Published 2016 Oct 6.
17. Fasanelli F, Giraudo MT, Ricceri F, Valeri L, Zugna D. Marginal Time-Dependent Causal Effects in Mediation Analysis With Survival Data. *Am J Epidemiol*. 2019;188(5):967-974.
18. Vanderweele TJ, Vansteelandt S. Odds ratios for mediation analysis for a dichotomous outcome. *Am J Epidemiol*. 2010;172(12):1339-1348.
19. Trichopoulos A, Kouris-Blazos A, Wahlqvist ML, Gnardellis C, Laggiou P, Polychronopoulos E, *et al.* Diet and overall survival in elderly people. *BMJ*. 1995;311(7018):1457-1460.
20. Allen L, Williams J, Townsend N, Mikkelsen B, Roberts N, Foster C, *et al.* Socioeconomic status and non-communicable disease behavioural risk factors in low-income and lower-middle-income countries: a systematic review. *Lancet Glob Health*. 2017;5(3):e277-e289.
21. dos Santos Silva I, Beral V. Socioeconomic differences in reproductive behaviour. *IARC Sci Publ*. 1997;(138):285-308.
22. Poorolajal J, Moradi L, Mohammadi Y, Cheraghi Z, Gohari-Ensaf F. Risk factors for stomach cancer: a systematic review and meta-analysis. *Epidemiol Health*. 2020;42:e2020004.
23. Carr S, Smith C, Wernberg J. Epidemiology and Risk Factors of Melanoma. *Surg Clin North Am*. 2020;100(1):1-12.
24. O'Keeffe LM, Taylor G, Huxley RR, Mitchell P, Woodward M, Peters SAE. Smoking as a risk factor for lung cancer in women and men: a systematic review and meta-analysis. *BMJ Open*. 2018;8(10):e021611. Published 2018 Oct 3.
25. Al-Bayati O, Hasan A, Pruthi D, Kaushik D, Liss MA. Systematic review of modifiable risk factors for kidney cancer. *Urol Oncol*. 2019;37(6):359-371.
26. Lenis AT, Lec PM, Chamie K, Mshs MD. Bladder Cancer: A Review. *JAMA*. 2020;324(19):1980-1991.

27. Kerr J, Anderson C, Lippman SM. Physical activity, sedentary behaviour, diet, and cancer: an update and emerging new evidence. *Lancet Oncol.* 2017;18(8):e457-e471.
28. Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50302 women with breast cancer and 96973 women without the disease. *Lancet.* 2002;360(9328):187-195.
29. Mihor A, Tomsic S, Zagar T, Lokar K, Zadnik V. Socioeconomic inequalities in cancer incidence in Europe: a comprehensive review of population-based epidemiological studies. *Radiol Oncol.* 2020;54(1):1-13. Published 2020 Feb 19.
30. Bryere J, Dejardin O, Launay L, Colonna M, Grosclaude P, Launoy G, *et al.* Socioeconomic status and site-specific cancer incidence, a Bayesian approach in a French Cancer Registries Network study. *Eur J Cancer Prev.* 2018;27(4):391-398.
31. Spadea T, Zengarini N, Kunst A, Zanetti R, Rosso S, Costa G. Cancer risk in relationship to different indicators of adult socioeconomic position in Turin, Italy. *Cancer Causes Control.* 2010;21(7):1117-1130.
32. Hoebel J, Kroll LE, Fiebig J, Lampert T, Katalinic A, Barnes B, *et al.* Socioeconomic Inequalities in Total and Site-Specific Cancer Incidence in Germany: A Population-Based Registry Study. *Front Oncol.* 2018;8:402. Published 2018 Sep 25.
33. Public Health England. National Cancer Intelligence Network. Cancer by deprivation in England. Incidence, 1996-2010. Mortality, 1997-2011. London: PHE; 2014
34. Walsh PM, McDevitt J, Deady S, O'Brien K & Comber H. Cancer inequalities in Ireland by deprivation, urban/rural status and age: a report by the National Cancer Registry. National Cancer Registry, Cork, Ireland. 2016
35. Hemminki K, Li X. Level of education and the risk of cancer in Sweden. *Cancer Epidemiol Biomarkers Prev.* 2003;12(8):796-802.
36. Vidarsdottir H, Gunnarsdottir HK, Olafsdottir EJ, Olafsdottir GH, Pukkala E, Tryggvadottir L. Cancer risk by education in Iceland; a census-based cohort study. *Acta Oncol.* 2008;47(3):385-390.
37. Smailyte G, Jasilionis D, Vincerzevskiene I, Krilaviciute A, Ambrozaitiene D, Stankuniene V, *et al.* Educational differences in incidence of cancer in Lithuania, 2001-2009: evidence from census-linked cancer registry data. *Eur J Cancer Prev.* 2015;24(3):261-266.
38. Berger E, Maitre N, Romana Mancini F, Baglietto L, Perduca V, Colineaux H, *et al.* The impact of lifecourse socio-economic position and individual social mobility on breast cancer risk. *BMC Cancer.* 2020;20(1):1138. Published 2020 Nov 23.

39. Gallo V, Mackenbach JP, Ezzati M, Menvielle G, Kunst AE, Rohrmann S, *et al.* Social inequalities and mortality in Europe--results from a large multi-national cohort. *PLoS One.* 2012;7(7):e39013.
40. Nagel G, Peter R, Braig S, Hermann S, Rohrmann S, Linseisen J. The impact of education on risk factors and the occurrence of multimorbidity in the EPIC-Heidelberg cohort. *BMC Public Health.* 2008;8:384. Published 2008 Nov 11.
41. Sacerdote C, Ricceri F, Rolandsson O, Baldi I, Chirilaque MD, Feskens E, *et al.* Lower educational level is a predictor of incident type 2 diabetes in European countries: the EPIC-InterAct study. *Int J Epidemiol.* 2012;41(4):1162-1173.
42. Rota M, Alicandro G, Pelucchi C, Bonzi R, Bertuccio P, Hu J, *et al.* Education and gastric cancer risk-An individual participant data meta-analysis in the StoP project consortium [published correction appears in Int J Cancer. 2020 Jun 1;146(11):E6]. *Int J Cancer.* 2020;146(3):671-681.
43. Aragonés N, Pérez-Gómez B, Pollán M, Ramis R, Vidal E, Lope V, *et al.* The striking geographical pattern of gastric cancer mortality in Spain: environmental hypotheses revisited. *BMC Cancer.* 2009;9:316. Published 2009 Sep 8.
44. Buffart TE, Louw M, van Grieken NC, Tijssen M, Carvalho B, Ylstra B, *et al.* Gastric cancers of Western European and African patients show different patterns of genomic instability. *BMC Med Genomics.* 2011;4:7. Published 2011 Jan 13.
45. Menvielle G, Boshuizen H, Kunst AE, Dalton SO, Vineis P, Bergmann MM, *et al.* The role of smoking and diet in explaining educational inequalities in lung cancer incidence. *J Natl Cancer Inst.* 2009;101(5):321-330.
46. Cumberbatch MGK, Jubber I, Black PC, Esperto F, Figueroa JD, Kamat AM, *et al.* Epidemiology of Bladder Cancer: A Systematic Review and Contemporary Update of Risk Factors in 2018. *Eur Urol.* 2018;74(6):784-795.
47. Braaten T, Weiderpass E, Kumle M, Lund E. Explaining the socioeconomic variation in cancer risk in the Norwegian Women and Cancer Study [published correction appears in Cancer Epidemiol Biomarkers Prev. 2006 Jan;15(1):187]. *Cancer Epidemiol Biomarkers Prev.* 2005;14(11 Pt 1):2591-2597.
48. Ortiz CA, Goodwin JS, Freeman JL. The effect of socioeconomic factors on incidence, stage at diagnosis and survival of cutaneous melanoma. *Med Sci Monit.* 2005;11(5):RA163-RA172.
49. Palme M, Simeonova E. Does women's education affect breast cancer risk and survival? Evidence from a population based social experiment in education. *J Health Econ.* 2015;42:115-124.
50. Neels K, Murphy M, Ní Bhrolcháin M, Beaujouan É. Rising Educational Participation and the Trend to Later Childbearing. *Popul Dev Rev.* 2017;43(4):667-693.

51. Hvidtfeldt UA. Mechanisms underlying social inequality in post-menopausal breast cancer. *Dan Med J*. 2014;61(10):B4922.
52. Vineis P, Perera F. Molecular epidemiology and biomarkers in etiologic cancer research: the new in light of the old [published correction appears in *Cancer Epidemiol Biomarkers Prev*. 2007 Dec;16(12):2797]. *Cancer Epidemiol Biomarkers Prev*. 2007;16(10):1954-1965.
53. Velasco V, Gragnano A, Gruppo Regionale Hbse Lombardia, Vecchio LP. Health Literacy Levels among Italian Students: Monitoring and Promotion at School. *Int J Environ Res Public Health*. 2021;18(19):9943. Published 2021 Sep 22.

Table 1 Descriptive analyses of the EPIC population in terms of demographic, clinical, and risk/protective factors for cancer, according to the Relative Index of Inequality Tertiles.

	<b>1<sup>st</sup> RIIT (High EL)</b> N (%) Mean (SD)	<b>2<sup>nd</sup> RIIT (Medium EL)</b> N (%) Mean (SD)	<b>3<sup>rd</sup> RIIT (Low EL)</b> N (%) Mean (SD)
<b>N</b>	147,277	152,385	146,389
<b>Age at recruitment (years)</b>	50.20 (9.66)	51.19 (9.50)	51.61 (9.68)
<b>Sex</b>			
<i>Female</i>	106,017 ( 72.0)	106,501 ( 69.9)	101,521 ( 69.4)
<b>Country</b>			
<i>France</i>	24,463 ( 16.6)	20,614 ( 13.5)	20,908 ( 14.3)
<i>Italy</i>	13,899 ( 9.4)	11,778 ( 7.7)	19,725 ( 13.5)
<i>Spain</i>	11,948 ( 8.1)	16,325 ( 10.7)	12,242 ( 8.4)
<i>United Kingdom</i>	25,162 ( 17.1)	20,150 ( 13.2)	21,975 ( 15.0)
<i>The Netherlands</i>	9,895 ( 6.7)	15,088 ( 9.9)	12,166 ( 8.3)
<i>Germany</i>	17,442 ( 11.8)	17,402 ( 11.4)	14,661 ( 10.0)
<i>Sweden</i>	15,790 ( 10.7)	15,557 ( 10.2)	18,098 ( 12.4)
<i>Denmark</i>	14,471 ( 9.8)	23,053 ( 15.1)	18,573 ( 12.7)
<i>Norway</i>	14,207 ( 9.6)	12,418 ( 8.1)	8,041 ( 5.5)
<b>Highest School Level</b>			
<i>None</i>	0 ( 0.0)	1,893 ( 1.2)	14,024 ( 9.6)
<i>Primary school completed</i>	3,179 ( 2.2)	15,207 (10.0)	97,749 (66.8)
<i>Technical/professional school</i>	3,841 ( 2.6)	82,546 (54.2)	20,887 (14.3)
<i>Secondary school</i>	31,139 (21.1)	50,970 (33.4)	13,729 ( 9.4)
<i>Longer education (incl. University deg)</i>	109,118 (74.1)	1,769 ( 1.2)	0 ( 0.0)
<b>Malignant Cancer (Number and % of Cases for each site)</b>			
<i>Stomach</i>	211 ( 0.1)	343 ( 0.2)	371 ( 0.3)
<i>Colorectal</i>	1,881 ( 1.3)	2,141 ( 1.4)	2,160 ( 1.5)
<i>Lung</i>	802 ( 0.5)	1,207 ( 0.8)	1,806 ( 1.2)
<i>Melanoma</i>	1,527 ( 1.0)	1,504 ( 1.0)	1,341 ( 0.9)
<i>Kidney</i>	304 ( 0.2)	331 ( 0.2)	369 ( 0.3)
<i>Bladder</i>	400 ( 0.3)	443 ( 0.3)	575 ( 0.4)
<i>Lymphoma</i>	669 ( 0.5)	816 ( 0.5)	838 ( 0.6)
<b>Time of Observation (days)</b>	5,135.84 (1,431.12)	5,181.07 (1,443.70)	5,152.62 (1,488.29)
<b>Smoking status</b>			
<i>Never</i>	74,130 ( 51.2)	73,480 ( 48.9)	69,183 ( 48.0)
<i>Former</i>	42,839 ( 29.6)	40,591 ( 27.0)	37,726 ( 26.2)
<i>Current</i>	27,769 ( 19.2)	36,143 ( 24.1)	37,194 ( 25.8)
<b>Alcohol consumption (g/day)</b>			
<i>&lt;1</i>	29,241 ( 19.9)	35,173 ( 23.3)	42,701 ( 29.7)

<i>1-12 / 1-24</i>	74,606 ( 50.8)	76,273 ( 50.5)	68,260 ( 47.5)
<i>&gt;=12 / &gt;=24</i>	42,897 ( 29.2)	39,684 ( 26.3)	32,833 ( 22.8)
<b>Mediterranean Diet Score (Trichopoulou score&gt;=4)</b>	72,435 (49.4)	65,794 (43.5)	63,079 (43.9)
<b>METS recreational activity</b>			
<i>&lt;=12 / &lt;=13.5</i>	28,326 ( 22.6)	29,431 ( 23.0)	38,256 ( 29.8)
<i>12-24 / 13.5-27</i>	32,885 ( 26.3)	32,460 ( 25.4)	31,552 ( 24.6)
<i>24-42 / 27-45</i>	32,783 ( 26.2)	32,468 ( 25.4)	28,827 ( 22.5)
<i>&gt;=42 / &gt;=45</i>	31,087 ( 24.9)	33,557 ( 26.2)	29,666 ( 23.1)
<b>BMI (kg/m<sup>2</sup>)</b>			
<i>&lt;=25</i>	90,254 ( 61.3)	79,071 ( 51.9)	67,327 ( 46.0)
<i>&gt;25 &lt;=30</i>	44,712 ( 30.4)	54,256 ( 35.6)	54,584 ( 37.3)
<i>&gt;30</i>	12,311 ( 8.4)	19,058 ( 12.5)	24,478 ( 16.7)
<b>Hypertension (yes)</b>	22,481 ( 17.6)	28,652 ( 22.4)	28,942 ( 24.5)

Abbreviations: RIIT= Relative Index of Inequality Tertiles, EL=Educational Level, METS=Metabolic Equivalents, BMI=Body Mass Index

Table 2 Cox Proportional-Hazard models to estimate the Hazard Ratios of belonging to the 2<sup>nd</sup> or 3<sup>rd</sup> tertile of the Relative Index of Inequality, meaning the medium and the lowest educational levels, respectively, compared to the 1<sup>st</sup> one, meaning the highest educational level, for the incidence of site-specific tumours, adjusted for age, country, and sex.

		All			Male			Female		
		HR	(95% CI)		HR	(95% CI)		HR	(95% CI)	
Stomach	2 <sup>nd</sup> vs 1 <sup>st</sup> RIIT	1.57	1.32	1.86	1.65	1.30	2.09	1.47	1.14	1.90
	3 <sup>rd</sup> vs 1 <sup>st</sup> RIIT	1.50	1.27	1.78	1.59	1.26	2.00	1.42	1.10	1.83
Colorectal	2 <sup>nd</sup> vs 1 <sup>st</sup> RIIT	1.05	0.99	1.12	1.11	1.01	1.22	1.01	0.93	1.09
	3 <sup>rd</sup> vs 1 <sup>st</sup> RIIT	1.01	0.95	1.08	1.04	0.95	1.15	0.99	0.91	1.07
Lung	2 <sup>nd</sup> vs 1 <sup>st</sup> RIIT	1.36	1.24	1.49	1.35	1.19	1.54	1.33	1.17	1.51
	3 <sup>rd</sup> vs 1 <sup>st</sup> RIIT	1.93	1.77	2.10	1.99	1.77	2.23	1.86	1.65	2.10
Melanoma	2 <sup>nd</sup> vs 1 <sup>st</sup> RIIT	0.92	0.86	0.99	0.88	0.79	0.99	0.96	0.88	1.06
	3 <sup>rd</sup> vs 1 <sup>st</sup> RIIT	0.79	0.74	0.86	0.75	0.67	0.84	0.83	0.75	0.91
Breast (for F: post, peri or surgical menopausal)	2 <sup>nd</sup> vs 1 <sup>st</sup> RIIT				1.24	0.50	3.10	0.98	0.94	1.00
	3 <sup>rd</sup> vs 1 <sup>st</sup> RIIT				1.21	0.48	3.03	0.87	0.84	0.90
Uterine body	2 <sup>nd</sup> vs 1 <sup>st</sup> RIIT							0.99	0.88	1.10
	3 <sup>rd</sup> vs 1 <sup>st</sup> RIIT							1.00	0.89	1.12
Ovary	2 <sup>nd</sup> vs 1 <sup>st</sup> RIIT							1.03	0.90	1.17
	3 <sup>rd</sup> vs 1 <sup>st</sup> RIIT							1.02	0.89	1.16
Prostate	2 <sup>nd</sup> vs 1 <sup>st</sup> RIIT				0.92	0.86	0.97			
	3 <sup>rd</sup> vs 1 <sup>st</sup> RIIT				0.88	0.83	0.93			
Kidney	2 <sup>nd</sup> vs 1 <sup>st</sup> RIIT	1.03	0.88	1.21	0.93	0.76	1.15	1.17	0.92	1.50
	3 <sup>rd</sup> vs 1 <sup>st</sup> RIIT	1.09	0.93	1.27	0.88	0.72	1.09	1.41	1.12	1.78
Bladder	2 <sup>nd</sup> vs 1 <sup>st</sup> RIIT	1.11	0.97	1.27	1.15	0.98	1.35	0.99	0.76	1.27
	3 <sup>rd</sup> vs 1 <sup>st</sup> RIIT	1.16	1.02	1.32	1.19	1.03	1.39	1.05	0.82	1.33
Lymphoma	2 <sup>nd</sup> vs 1 <sup>st</sup> RIIT	1.14	1.03	1.27	1.15	0.99	1.34	1.13	0.98	1.30
	3 <sup>rd</sup> vs 1 <sup>st</sup> RIIT	1.10	0.99	1.22	1.08	0.92	1.25	1.12	0.97	1.28

Abbreviations: RIIT= Relative Index of Inequality Tertile, HR= Hazard Ratio



Table 3 Mediators considered in the mediation analyses for each cancer site associated with the Relative Index of Inequality in the Cox proportional hazard models.

<b>Cancer Site</b>	<b>Mediators</b>	<b>Details</b>
<i>Stomach</i>	Smoking status	<i>Never, Former, Current</i>
	Alcohol consumption	<i>In Men: &lt;1, 1-24, &gt;=24 g/day In Women: &lt;1, 1-12, &gt;=12 g/day</i>
	Mediterranean Diet adherence	<i>Trichopoulou score (continuous numerical score between 0 and 7), which considered 8 components of the Mediterranean diet</i>
	BMI	<i>&lt;=25, 25-30, &gt;30 (kg/m<sup>2</sup>)</i>
<i>Melanoma</i>	Smoking status	<i>Never, Former, Current</i>
	METS recreational activity	<i>In Men: &lt;13.5, 13.5-27, 27-45, &gt;=45 In Women: &lt;12, 12-24, 24-42, &gt;=42</i>
<i>Lung</i>	Smoking status	<i>Never, Former, Current</i>
<i>Kidney</i>	Smoking status	<i>Never, Former, Current</i>
	BMI	<i>&lt;=25, 25-30, &gt;30 kg/m<sup>2</sup></i>
	Hypertension	<i>Yes/No</i>
<i>Bladder</i>	Smoking status	<i>Never, Former, Current</i>
<i>Breast (just considering post. peri or surgical menopausal women)</i>	Smoking status	<i>Never, Former, Current</i>
	Alcohol consumption	<i>&lt;1, 1-12, &gt;=12 g/day</i>
	Mediterranean Diet adherence	<i>Trichopoulou score (continuous numerical score between 0 and 7), which considered 8 components of the Mediterranean diet</i>
	BMI	<i>&lt;=25, 25-30, &gt;30 kg/m<sup>2</sup></i>
	Reproductive history	<i>Nulliparous, age at first full term pregnancy &lt;=25, 25-36, &gt;36</i>
	Breast feeding	<i>Yes/No</i>

Abbreviations: METS=Metabolic Equivalent, BMI=Body Mass Index

Table 4 Mediation analyses results: the reported Hazard Ratios, computed at the median of the follow-up time, are the effects (pure direct, total indirect, and total effects) estimated as functions of time to event (years), considering cancer occurrence at specific site as outcomes, Relative Index of Inequality (RII) (2<sup>nd</sup> or 3<sup>rd</sup> tertile of RII, meaning the medium and the lowest educational levels, respectively, compared to the 1<sup>st</sup> one, meaning the highest educational level) as exposure and site-specific risk/protective factors as mediators. Confidence Intervals were built using the 95% percentile bootstrap method.

			all				Male				Female			
			HR	(95% CI)		PM	HR	(95% CI)		PM	HR	(95% CI)		PM
Stomach cancer	Total effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	1.41	1.20	1.68		1.54	1.22	2.00		1.47	1.15	1.96	
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	1.55	1.32	1.85		1.58	1.26	1.99		1.56	1.21	2.02	
	Pure Direct effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	1.51	1.27	1.81		1.57	1.23	2.02		1.45	1.13	1.94	
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	1.42	1.21	1.70		1.51	1.19	1.92		1.34	1.04	1.74	
	Total Indirect effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	0.94	0.91	0.96	-	0.99	0.95	1.01	-3%	1.02	0.97	1.07	6%
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	1.09	1.06	1.12	23%	1.05	1.00	1.10	13%	1.16	1.10	1.23	39%
Lung Cancer	Total effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	1.31	1.20	1.44		1.33	1.17	1.52		1.47	1.30	1.68	
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	1.99	1.83	2.17		2.00	1.79	2.27		2.04	1.80	2.31	
	Pure Direct effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	1.23	1.13	1.34		1.18	1.05	1.35		1.23	1.09	1.41	
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	1.62	1.49	1.76		1.64	1.47	1.86		1.56	1.38	1.76	
	Total Indirect effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	1.07	1.05	1.09	27%	1.12	1.10	1.15	44%	1.19	1.16	1.23	50%
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	1.23	1.21	1.25	38%	1.22	1.19	1.24	36%	1.3	1.27	1.33	46%
Melanoma	Total effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	0.9	0.83	0.97		0.90	0.79	1.01		0.97	0.88	1.07	
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	0.83	0.76	0.89		0.80	0.70	0.90		0.85	0.77	0.94	
	Pure Direct effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	0.96	0.88	1.03		0.94	0.83	1.06		0.99	0.9	1.09	
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	0.83	0.76	0.89		0.8	0.71	0.9		0.85	0.77	0.94	
	Total Indirect effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	0.94	0.93	0.95	59%	0.96	0.94	0.97	39%	0.98	0.96	1.00	-
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	1.00	0.99	1.01	0%	1.00	0.98	1.02	0%	1.00	0.98	1.01	0%
Breast Cancer <i>(just considering post. peri or surgical menopausal women)</i>	Total effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII									1.03	0.97	1.08	
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII									0.89	0.84	0.94	
	Pure Direct effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII									1.02	0.96	1.07	
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII									0.93	0.88	0.98	
	Total Indirect effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII									1.01	1.00	1.02	-
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII									0.95	0.94	0.97	40%
Kidney Cancer	Total effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	0.91	0.76	1.08		0.89	0.72	1.11		1.09	0.82	1.43	
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	1.06	0.88	1.25		0.84	0.66	1.05		1.50	1.16	2.00	
	Pure Direct effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	0.93	0.78	1.13		0.87	0.70	1.09		1.02	0.78	1.37	
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	0.94	0.78	1.11		0.77	0.61	0.98		1.21	0.93	1.61	
	Total Indirect effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	0.98	0.95	1.01	-	1.02	0.99	1.06	-	1.07	1.02	1.13	-
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	1.13	1.09	1.17	-	1.09	1.03	1.15	-	1.24	1.16	1.32	58%
Bladder cancer	Total effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	0.95	0.82	1.09		1.14	0.97	1.35		0.88	0.67	1.14	
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	1.24	1.09	1.42		1.31	1.12	1.53		1.16	0.90	1.50	
	Pure Direct effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	1.07	0.92	1.22		1.09	0.93	1.29		0.98	0.74	1.26	
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	1.09	0.96	1.25		1.10	0.93	1.29		1.03	0.80	1.33	
	Total Indirect effect	2 <sup>nd</sup> vs 1 <sup>st</sup> RII	0.89	0.87	0.91	-	1.04	1.02	1.07	-	0.91	0.85	0.96	-
		3 <sup>rd</sup> vs 1 <sup>st</sup> RII	1.13	1.11	1.15	61%	1.19	1.17	1.22	68%	1.13	1.09	1.16	-

Abbreviations: PM=Proportion Mediated, RII=Relative Index of Inequality Tertile, HR= Hazard Ratio, CI= Confidence Intervals

Figure 1: Directed Acyclic Graph (DAG) describing the assumed relationships considered for mediation analyses

1

