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

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

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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 ofthyroid, 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 wereadjusted 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:

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

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].

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Disclaimer

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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.

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

1-12 / 1-24	74,606 (50.8)	76,273 (50.5)	68,260 (47.5)
>=12 / >=24	42,897 (29.2)	39,684 (26.3)	32,833 (22.8)
Mediterranean Diet Score (*Trichopoulou score>=4)*	72,435 (49.4)	65,794 (43.5)	63,079 (43.9)
METS recreational activity			
<=12 / <=13.5	28,326 (22.6)	29,431 (23.0)	38,256 (29.8)
12-24 / 13.5-27	32,885 (26.3)	32,460 (25.4)	31,552 (24.6)
24-42 / 27-45	32,783 (26.2)	32,468 (25.4)	28,827 (22.5)
>=42 / >=45	31,087 (24.9)	33,557 (26.2)	29,666 (23.1)
BMI *(kg/m^2)*			
<=25	90,254 (61.3)	79,071 (51.9)	67,327 (46.0)
>25 <=30	44,712 (30.4)	54,256 (35.6)	54,584 (37.3)
>30	12,311 (8.4)	19,058 (12.5)	24,478 (16.7)
Hypertension *(yes)*	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 2nd or 3rd tertile of the Relative Index of Inequality, meaning the medium and the lowest educational levels, respectively, compared to the 1st 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	**2nd vs 1st RIIT**	1.57	1.32	1.86		1.65	1.30	2.09		1.47	1.14	1.90
	3rd vs 1st RIIT	1.50	1.27	1.78		1.59	1.26	2.00		1.42	1.10	1.83
Colorectal	**2nd vs 1st RIIT**	1.05	0.99	1.12		1.11	1.01	1.22		1.01	0.93	1.09
	3rd vs 1st RIIT	1.01	0.95	1.08		1.04	0.95	1.15		0.99	0.91	1.07
Lung	**2nd vs 1st RIIT**	1.36	1.24	1.49		1.35	1.19	1.54		1.33	1.17	1.51
	3rd vs 1st RIIT	1.93	1.77	2.10		1.99	1.77	2.23		1.86	1.65	2.10
Melanoma	**2nd vs 1st RIIT**	0.92	0.86	0.99		0.88	0.79	0.99		0.96	0.88	1.06
	3rd vs 1st 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)	**2nd vs 1st RIIT**					1.24	0.50	3.10		0.98	0.94	1.00
	3rd vs 1st RIIT					1.21	0.48	3.03		0.87	0.84	0.90
Uterine body	**2nd vs 1st RIIT**									0.99	0.88	1.10
	3rd vs 1st RIIT									1.00	0.89	1.12
Ovary	**2nd vs 1st RIIT**									1.03	0.90	1.17
	3rd vs 1st RIIT									1.02	0.89	1.16
Prostate	**2nd vs 1st RIIT**					0.92	0.86	0.97				
	3rd vs 1st RIIT					0.88	0.83	0.93				
Kidney	**2nd vs 1st RIIT**	1.03	0.88	1.21		0.93	0.76	1.15		1.17	0.92	1.50
	3rd vs 1st RIIT	1.09	0.93	1.27		0.88	0.72	1.09		1.41	1.12	1.78
Bladder	**2nd vs 1st RIIT**	1.11	0.97	1.27		1.15	0.98	1.35		0.99	0.76	1.27
	3rd vs 1st RIIT	1.16	1.02	1.32		1.19	1.03	1.39		1.05	0.82	1.33
Lymphoma	**2nd vs 1st RIIT**	1.14	1.03	1.27		1.15	0.99	1.34		1.13	0.98	1.30
	3rd vs 1st 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.

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

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

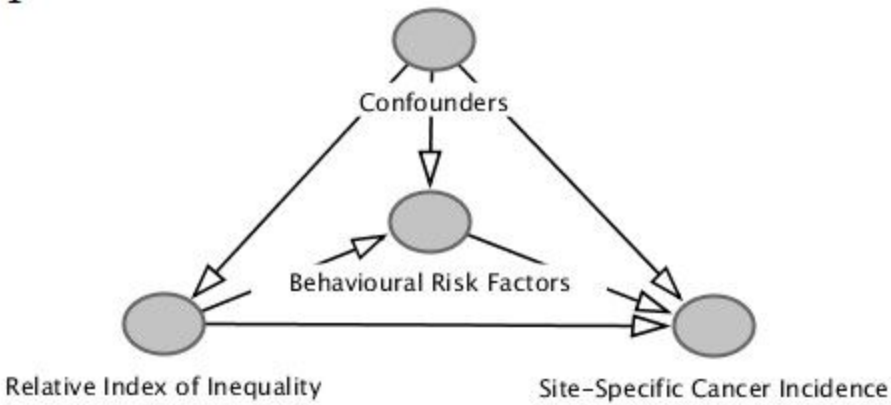
Table 4 Mediation analyses results: the reported Hazard Ratios, computed at the median of the follow-up time, are the effects (pure direct, total indirect, and total effects) estimated as functions of time to event (years), considering cancer occurrence at specific site as outcomes, Relative Index of Inequality (RII) (2^{nd} or 3^{rd} tertile of RII, meaning the medium and the lowest educational levels, respectively, compared to the 1^{st} 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^{nd} vs 1^{st} RIIT**	1.41	1.20	1.68		1.54	1.22	2.00		1.47	1.15	1.96	
		3^{rd} vs 1^{st} RIIT	1.55	1.32	1.85		1.58	1.26	1.99		1.56	1.21	2.02	
	Pure Direct effect	**2^{nd} vs 1^{st} RIIT**	1.51	1.27	1.81		1.57	1.23	2.02		1.45	1.13	1.94	
		3^{rd} vs 1^{st} RIIT	1.42	1.21	1.70		1.51	1.19	1.92		1.34	1.04	1.74	
	Total Indirect effect	**2^{nd} vs 1^{st} RIIT**	0.94	0.91	0.96	-	0.99	0.95	1.01	-3%	1.02	0.97	1.07	6%
		3^{rd} vs 1^{st} RIIT	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^{nd} vs 1^{st} RIIT**	1.31	1.20	1.44		1.33	1.17	1.52		1.47	1.30	1.68	
		3^{rd} vs 1^{st} RIIT	1.99	1.83	2.17		2.00	1.79	2.27		2.04	1.80	2.31	
	Pure Direct effect	**2^{nd} vs 1^{st} RIIT**	1.23	1.13	1.34		1.18	1.05	1.35		1.23	1.09	1.41	
		3^{rd} vs 1^{st} RIIT	1.62	1.49	1.76		1.64	1.47	1.86		1.56	1.38	1.76	
	Total Indirect effect	**2^{nd} vs 1^{st} RIIT**	1.07	1.05	1.09	27%	1.12	1.10	1.15	44%	1.19	1.16	1.23	50%
		3^{rd} vs 1^{st} RIIT	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^{nd} vs 1^{st} RIIT**	0.9	0.83	0.97		0.90	0.79	1.01		0.97	0.88	1.07	
		3^{rd} vs 1^{st} RIIT	0.83	0.76	0.89		0.80	0.70	0.90		0.85	0.77	0.94	
	Pure Direct effect	**2^{nd} vs 1^{st} RIIT**	0.96	0.88	1.03		0.94	0.83	1.06		0.99	0.9	1.09	
		3^{rd} vs 1^{st} RIIT	0.83	0.76	0.89		0.8	0.71	0.9		0.85	0.77	0.94	
	Total Indirect effect	**2^{nd} vs 1^{st} RIIT**	0.94	0.93	0.95	59%	0.96	0.94	0.97	39%	0.98	0.96	1.00	-
		3^{rd} vs 1^{st} RIIT	1.00	0.99	1.01	0%	1.00	0.98	1.02	0%	1.00	0.98	1.01	0%
Breast Cancer *(just considering post. peri or surgical menopausal women)*	**Total effect**	**2^{nd} vs 1^{st} RIIT**									1.03	0.97	1.08	
		3^{rd} vs 1^{st} RIIT									0.89	0.84	0.94	
	Pure Direct effect	**2^{nd} vs 1^{st} RIIT**									1.02	0.96	1.07	
		3^{rd} vs 1^{st} RIIT									0.93	0.88	0.98	
	Total Indirect effect	**2^{nd} vs 1^{st} RIIT**									1.01	1.00	1.02	-
		3^{rd} vs 1^{st} RIIT									0.95	0.94	0.97	40%
Kidney Cancer	**Total effect**	**2^{nd} vs 1^{st} RIIT**	0.91	0.76	1.08		0.89	0.72	1.11		1.09	0.82	1.43	
		3^{rd} vs 1^{st} RIIT	1.06	0.88	1.25		0.84	0.66	1.05		1.50	1.16	2.00	
	Pure Direct effect	**2^{nd} vs 1^{st} RIIT**	0.93	0.78	1.13		0.87	0.70	1.09		1.02	0.78	1.37	
		3^{rd} vs 1^{st} RIIT	0.94	0.78	1.11		0.77	0.61	0.98		1.21	0.93	1.61	
	Total Indirect effect	**2^{nd} vs 1^{st} RIIT**	0.98	0.95	1.01	-	1.02	0.99	1.06	-	1.07	1.02	1.13	-
		3^{rd} vs 1^{st} RIIT	1.13	1.09	1.17	-	1.09	1.03	1.15	-	1.24	1.16	1.32	58%
Bladder cancer	**Total effect**	**2^{nd} vs 1^{st} RIIT**	0.95	0.82	1.09		1.14	0.97	1.35		0.88	0.67	1.14	
		3^{rd} vs 1^{st} RIIT	1.24	1.09	1.42		1.31	1.12	1.53		1.16	0.90	1.50	
	Pure Direct effect	**2^{nd} vs 1^{st} RIIT**	1.07	0.92	1.22		1.09	0.93	1.29		0.98	0.74	1.26	
		3^{rd} vs 1^{st} RIIT	1.09	0.96	1.25		1.10	0.93	1.29		1.03	0.80	1.33	
	Total Indirect effect	**2^{nd} vs 1^{st} RIIT**	0.89	0.87	0.91	-	1.04	1.02	1.07	-	0.91	0.85	0.96	-
		3^{rd} vs 1^{st} RIIT	1.13	1.11	1.15	61%	1.19	1.17	1.22	68%	1.13	1.09	1.16	-

Abbreviations: PM=Proportion Mediated, RIIT=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


Confounders
Behavioural Risk Factors
Relative Index of Inequality
Site-Specific Cancer Incidence