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Lung cancer mortality in the European cohort of titanium dioxide workers: a re-analysis of the exposure-response relationship

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Accepted manuscript

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Running Head: Titanium dioxide exposure and lung cancer

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ABSTRACT

Objectives: Animal bioassays have demonstrated convincing evidence of the potential carcinogenicity to humans of titanium dioxide (TiO_2), but limitations in cohort studies have been identified, among which is the healthy worker survivor effect (HWSE). We aimed to address this bias in a pooled study of four cohorts of TiO_2 workers.

Methods: We re-analysed data on respirable TiO_2 dust exposure and lung cancer mortality among 7341 male workers employed in TiO_2 production in Finland, France, United Kingdom and Italy using the parametric g-formula, considering three hypothetical interventions: setting annual exposures at 2.4 (U.S. occupational exposure limit), 0.3 (German limit), and 0 mg/m^3 for 25 and 35 years.

Results: The HWSE was evidenced. Taking this into account, we observed a positive association between lagged cumulative exposure to TiO_2 and lung cancer mortality. The estimated number of lung cancer deaths at each age group decreased across increasingly stringent intervention levels. At age 70 years, the estimated number of lung cancer deaths expected in the cohort after 35-year exposure was 293 for exposure set at 2.4 mg/m^3, 235 for exposure set at 0.3 mg/m^3, and 211 for exposure set at 0 mg/m^3.

Conclusion: This analysis shows that HWSE can hide an exposure-response relationship. It also shows that TiO_2 epidemiological data could demonstrate an exposure-effects relationship if analysed appropriately. More epidemiological studies and similar re-analyses of existing cohort studies are warranted to corroborate the human carcinogenicity of TiO_2. This human evidence, when combined with the animal evidence, strengthens the overall evidence of carcinogenicity of TiO_2.

KEY WORDS

Accepted manuscript

Occupational exposure; g-formula; causal inference; retrospective cohort

INTRODUCTION

There is substantial interest in human evidence regarding the carcinogenicity of titanium dioxide (TiO_2), an odorless white pigment and opacifying agent widely used since the 1920s. TiO_2 is classified as possibly carcinogenic to humans by the International Agency for Research on Cancer based on sufficient evidence from cancer bioassay studies and inadequate evidence from human cancer studies. Since 2020, TiO_2 is also classified as a suspected human carcinogen by inhalation in the European Union according to Regulation n°1272/2008.

Prior large cohorts of TiO_2 workers reported increased mortality from lung cancer, but failed to observe an exposure–response relationship with cumulative exposure to TiO_2,[1] except in a French cohort of TiO_2 workers.[2] One of the key limitations noted in the occupational cohorts was the potential healthy worker survivor effect (HWSE) which can mask association between cumulative exposure and lung cancer mortality.[3] For instance, in the pooled European study of TiO_2 workers, a key study on this topic, no evidence of an association between respirable TiO_2 exposure and lung cancer mortality was observed despite the excess of lung cancer mortality among male TiO_2 workers as compared to the general population (standardised mortality ratio=1.23; 95% confidence interval (95%CI)=1.10-1.38).[4]

In this study, we re-analysed a subset of the pooled European cohort of TiO_2 workers,[4] to examine the evidence of HWSE and the exposure-response relationship between cumulative exposure to TiO_2 and lung cancer mortality. We implemented the g-computation algorithm formula (g-formula) recommended for statistical analysis of cohort data in the presence of time-varying confounders affected by prior exposure, typical of HWSE.[5] The g-formula has been proven to be an essential method for estimating human health effects of exposures and

Accepted manuscript

interventions on exposures in such scenarios.[5] Therefore, we applied it to assess the effect of three hypothetical interventions of TiO_2 exposure limitation.

METHODS

Study population

The original pooled European cohort included workers who had been employed at least 1 month in one of 11 TiO_2 production factories in six European countries (Finland, France, Italy, Norway, Germany, and the UK).[4] All female workers and male workers with missing death certificates and/or lacking quantitative exposure estimates were excluded from the exposure-response analysis of this cohort.[4] We used the same criteria of worker inclusion/exclusion as in original cohort, but restricted the study to four countries (Finland, France, Italy, and the UK), for which data were still available and ethical approvals obtained.

Exposure assessment

The factories produced mainly pigment-grade TiO_2, although TiO_2 form (e.g., particle size and crystalline phase) was ignored.[6] Information on demographic and employment characteristics was collected from factories' records describing date of birth, sex, race, and dates of hire, job or department change, and termination. Estimated cumulative occupational exposure to respirable TiO_2 dust was derived from job title and work history.[6] Exposure assessments were carried out at the level of occupational titles for each plant for discrete time periods throughout the history of plant operations. Lists of occupational titles were compiled and coded for each factory. Exposure measurement data were obtained from company files along with information such as the area(s) of the plant where measurements were made, the presence of any local ventilation, the type of the materials being handled and the purpose of sampling. These were then linked to the work history of each individual in the cohort to provide exposure estimates.

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Statistical analysis

The lengths of follow-up varied between countries and ranged from 1950–1972 until 1997–2001. The primary outcome of interest was death for which the underlying cause was attributed to cancers of the trachea, bronchus and lung (ICD-9 code 162).

A data tabulation of person-periods and events was constructed with one record for each person-year of observation from date of entry into the analysis until end of follow-up or administrative censoring of workers alive at age 90 years. Using the observed data, we fitted logistic regression models for the probability of the outcome of interest, for the probability of remaining at work, and for the probability of dying from a competing cause, as a function of covariates and estimated exposure. The cumulative TiO_2 exposure was 10-year lagged (Supplementary material Figure S1 and Technical Appendix 1).

The g-formula was implemented by a Monte Carlo simulation based on the regression model estimates of the probability of termination of employment and death.[5, 7] Ten Monte Carlo samples per exposure scenario were drawn randomly from the observed cohort and the estimated parameters from the parametric models to recreate the study data for each person in the sample under specified exposure intervention. Three hypothetical interventions were considered: setting workers' annual exposures to 2.4 mg/m^3, 0.3 mg/m^3 (the currently recommended TiO_2 occupational exposure limits in the US [8] and Germany [9], respectively), and zero exposure. For each intervention, we assumed two possible exposure durations: 25 and 35 years and estimated the expected lung cancer mortality at 60, 70, 80, and 90 years of age. The associated 95%-CIs were calculated using bootstrap samples.

RESULTS

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The cohort included 7341 workers (Table S2). At the end of the follow-up, 139 lung cancer deaths were observed. The presence of the HWSE was evident (Figure S1). Being in employment reduced the risk of lung cancer mortality (OR=0.14, 95%CI=0.08-0.22) and the probability of leaving the employment increased as a function of TiO_2 exposure (OR=3.55 95%CI=2.82-4.46)). The OR of lung cancer death associated with lagged cumulative exposure to TiO_2 was estimated at 1.03 per 1 mg/m^3-year (95%CI=0.99-1.07), after adjustment for the employment status in previous and current years and employment duration.

G-estimates of lung cancer mortality, derived under the three hypothetical interventions, are shown in Table 1. The estimated number of lung cancer deaths at 60, 70, 80, and 90 years of age all decrease across the three interventions considered and for both exposure durations.

DISCUSSION

This re-analysis provides the first evidence of an exposure-response relationship between TiO_2 cumulative exposure and lung cancer mortality using the parametric g-formula. Adjustment of a standard regression model for employment status orexposure duration is not sufficient for complete HWSE correction.[3] However, rank ordering of lung cancer deaths across levels of the intervention estimated by g-formula is consistent with a positive exposure-response association between TiO_2 and lung cancer (3% per 1 mg/m^3-year of respiratory TiO_2).

A limitation of the g-formula is the g-null paradox. The g-formula may be guaranteed some degree of model misspecification if there is treatment-confounder feedback and the sharp causal null hypothesis (i.e., the intervention has no effect on any individual's outcome at any time) holds.[10] To address concern that model misspecification may lead to bias, we followed recent guidance [11] to avoid overly parsimonious models for the components of the g-formula in this analysis.

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A causal interpretation of the findings requires certain statistical assumptions, including consistency, positivity, exchangeability.[12] The consistency assumption may be challenging given the complexity of historical exposure conditions and the various TiO_2forms, the latter being insufficiently documented. We nevertheless believe that exposure contrasts are defined here well enough to support meaningful inference regarding TiO_2's effect. The positivity hypothesis (i.e. observations on exposed and unexposed workers through covariate levels) was difficult to confirm as 82% of workers were exposed. However, the positive exposure-response relationship based on continuous cumulative lagged exposure to TiO_2 supports these assumptions.

The exchangeability assumption (i.e., no unmeasured confounding) is challenging given the limitations of available data on smoking. The most complete smoking data were available for the French cohort and showed no effect of adjustment for smoking on estimates of TiO_2-lung cancer mortality associations.[2] Moreover, we were able to assess some other occupational co-exposures that are suspected or known lung carcinogens, including asbestos, welding fumes, and other mineral dusts; adjustment for these exposures had no effect on the association with TiO_2.

A confounder typically of concern in occupational cohort mortality studies is the HWSE.[3] In the current study, this source of confounding was addressed by the g-formula. In prior analyses of these data using standard multivariable regression method, the association was likely masked by the HWSE and potentially the exposure misclassification in the early years of follow-up. Prior to undertaking the g-formula analysis, we assessed the most important HWSE components in these data and confirmed their presence. Moreover, prior reports of SMR analyses indicated patterns consistent with the HWSE[3] and in the analysis of the French cohort, duration of employment was negatively associated with lung cancer mortality.[2] These underscore the relevance of g-methods in these cohorts and future investigations of TiO_2's effects on human health.

Accepted manuscript

The estimates with overlapping CI are likely due to the limited statistical power in this study, which might be addressed by additional follow-up of these cohorts. More epidemiological studies and similar re-analyses of updated existing cohort studies are warranted to corroborate the human carcinogenicity of TiO_2. This human evidence, when combined with the animal evidence, strengthens the overall evidence of carcinogenicity of TiO_2.

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None.

CONTRIBUTORS

IGC designed and conducted this study and drafted the manuscript, AG-G, DBR, and PW conducted statistical analyses. KS and MSB centralised the data, facilitated data access, and obtained IARC ethical approval. SC, SFF, and CM contributed to study coordination and French ethical approval. All authors discussed the study methodology, read the manuscript, critically reviewed it and agreed on the final version.

FUNDING

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COMPETING INTERESTS

None declared.

PATIENT CONSENT FOR PUBLICATION

Not required.

ETHICS APPROVAL

The study was authorised by the IARC ethics Committee (IEC project number 18-32). The use of the data for the French cohort was approved by the French Data Protection Authority (CNIL), Authorisation No 999250. The use of the data for the UK cohort was approved by the EPS ethics

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committee of Heriot-Watt University (approval number 19/EA/JC/1). The use of the data for the Italian cohort was approved by the Comitato Etico Interaziendale A.S.L Citta di Torino (approval number CS2/1250). The use of the data for the Finnish cohort was approved by Statistics Finland (approval number TK-53-988-19).

DATA AVAILABILITY STATEMENT

Data may be obtained from a third party and are not publicly available.

KEY MESSAGES

What is already known about this subject?

Titanium dioxide (TiO_2) is classified by the International Agency for Research on Cancer as possibly carcinogenic to humans. In 2020, the European Chemicals Agency classified TiO_2 under all forms as suspected human carcinogen by inhalation. Prior large cohorts of TiO_2 workers reported increased mortality from lung cancer but failed to observe an exposure–response relationship with cumulative exposure to TiO_2, except in a French cohort of TiO2 workers. A concern of potential healthy worker survivor effect (HWSE) has been raised.

What are the new findings?

We re-analysed data from the European cohort of TiO_2 workers and found strong evidence of the HWSE. Taking this into account, a positive exposure–response relationship with 10-years lagged cumulative exposure to TiO_2 was observed. The estimated number of lung cancer deaths at each age group decreased across increasingly stringent exposure limits.

How might this impact on policy or clinical practice in the foreseeable future?

This analysis shows that HWSE can hide exposure-response relationship. It also shows that TiO_2 epidemiological data could demonstrate an exposure-effects relationship if analysed appropriately.

Accepted manuscript

This human evidence, when combined with the animal evidence, strengthens the overall evidence of carcinogenicity of TiO_2.

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Accepted manuscript

Table 1. Estimated cumulative lung cancer mortality at age 60, 70, 80 and 90 years under three hypothetical interventions on the TiO_2 exposure and assuming two durations of this exposure. European TiO_2 worker cohort, 1955-1990.

Attained age (in years)	Cumulative number of lung cancer deaths (95%CI) assuming 25-year exposure duration			Cumulative number of lung cancer deaths (95%CI) assuming 35-year exposure duration		
	Set exposure to 2.4 mg/m^3	Set exposure to 0.3 mg/m^3	Set exposure to 0.0 mg/m^3	Set exposure to 2.4 mg/m^3	Set exposure to 0.3 mg/m^3	Set exposure to 0.0 mg/m^3
60	50 (46-55)	38 (33-44)	39 (34-45)	98 (94-102)	79 (72-86)	74 (68-80)
70	134 (130-139)	105 (97-112)	95 (86-104)	293 (288-299)	235 (226-243)	211 (200-223)
80	168 (162-174)	128 (121-136)	116 (107-125)	417 (407-427)	329 (320-337)	299 (281-316)
90	169 (163-174)	129 (121-136)	116 (108-125)	423 (412-433)	333 (325-342)	303 (286-321)

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ONLINE SUPPLEMENTARY MATERIAL

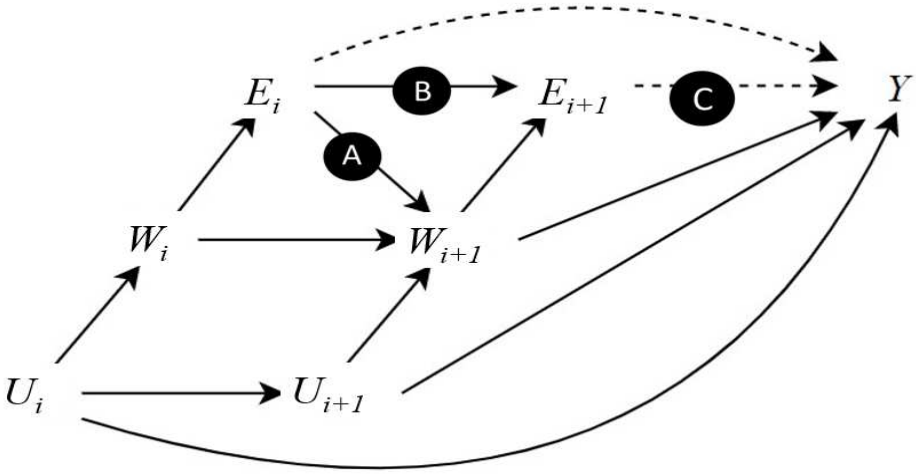

Figure S1. Directed acyclic graph representing structural relationships underlying the healthy worker survivor effect.

This graph represents the evolution over a worker's lifetime of his or her employment status (1 if employed, 0 if terminated), exposure and mortality from lung cancer (1 if the cause of death is lung cancer, 0 for any other situation) as well as the presumed causal links between these factors. Dashed lines show causal effect of the exposure. A, B, and C represent relationships necessary to model for implementation of the g-formula to control for potential confounding bias due to the healthy worker survival effect. E_i corresponds to exposure to TiO_2 in year i; W_i corresponds to employment status and U_i to health status in year i. Finally, Y denotes mortality from lung cancer. The unmeasured health status U_i in year i influences employment status in the same year and health status U_i+1 in the next year. Similarly, $W_i$influences E_i and W_i+1. Finally, E_i affects E_i+1. Note that this is a simplified directed acyclic graph showing only two time intervals and omitting the baseline covariates.

Accepted manuscript

Technical Appendix 1.

Given the objectives of the project, the choice of the g-formula seemed the most judicious, as it is the only method allowing the evaluation of the effect of hypothetical interventions. To apply this method we began by modeling the different presumed causal associations presented in Figure S1: the association between employment status and survival, the association between previous exposure to TiO_2 and current employment status. The third key component association (i.e., an association between employment status and subsequent exposure) is considered deterministic, because the end of employment leads to the end of exposure. For this, the following models were applied to the observed data in the study population (pooled cohort of four countries, n=7341):

1. A logistic regression model to predict the probability of job termination for a given person-year (W_i+1 as a function of W_i and E_i);
2. A logistic regression model to predict exposure in that year (E_i+1 as a function of W_i and E_i when W_i+1 =1) and a linear regression model to predict exposure level (as a function of active employment and exposure);
3. A logistic regression model to predict lung cancer death as a function of employment status and exposure (Y as a function of E_i);
4. A logistic regression model for other causes of death.

The beta coefficients of all variables included in each of these models are provided in the technical report of the study[1], available upon request to the corresponding author.

[1] Irina Guseva Canu, Alan Gaillen-Guedy, Ahti Anttila, Danièle Luce, Damien McElvenny, Franco Merletti, Eero Pukkala, Mary Schubauer-Berigan, Kurt Straif, Pascal Wild, David B. Richardson. Rapport des résultats du projet scientifique « RealyTi » Reanalysis of human TiO2 data. Troisième version. 22 décembre 2020. 66p.

Accepted manuscript

In a second step, we used the results of these models to estimate the potential effect of different exposure scenarios. The results of this step were expressed in terms of estimated number of deaths per attained age for each hypothetical intervention on the exposure.

We considered three hypothetical interventions:

- A first intervention sets the annual respiratory TiO_2 exposure at 2.4 mg/m^3
- A second intervention sets the annual respiratory TiO_2 exposure at 0.3 mg/m^3
- A third intervention sets the exposures of all subjects during their entire career to zero

These first two values correspond to the currently recommended OELs for TiO_2 fine dust (respirable fraction) in the USA and Germany, respectively.

The occupational careers, dates of death and dates of lung cancer death of the cohort participants were resampled (Monte Carlo) 10 times for each scenario, resulting in 10 pseudo-cohorts for each scenario.

In practice, we retained information on the baseline variables for each participant (identification number, year of hire, age at hire, exposure at the start of follow-up, center identification code in each country) and drew, year by year, exposure status, cumulative exposure level fixed by exposure scenario lung cancer death (yes/no), and, if applicable, death by another cause of death (concurrent causes).

Specifically, from year m=1, employment status is assigned using the conditional probability, estimated from the parametric employment status model. If the person is employed, the exposure of this person is defined at the specified level by a new simulation. Then, the probability of lung cancer and competing causes of death is estimated based on the joint distribution of exposure and covariates. A binary indicator for each outcome is drawn from a Bernoulli distribution with the

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associated probability. If the individual is still alive at the end of year m, the process is repeated for m + 1, until death or the end of follow-up date. Within each person-year, we assume the temporal order of the component variables assigned to each person-year as follows: fixed covariates, employment status, conditional TiO_2 exposure, lung cancer death, and death from another cause.

The final step was to calculate for each simulated joint pseudo-cohort the number of deaths in each age group assuming 25 and 35-year exposure.

In order to select the most relevant explanatory variables for each of the four models explained above, we based ourselves on *Akaike Information Criterion* (AIC). This criterion is based on a compromise between the quality of the fit and the complexity of the model. This penalizes models with a large number of variables to limit the effects of over-fitting. The model with the lowest AIC value was therefore considered the best for predicting employment status, exposure status, cumulative exposure, and lung cancer death and death from other causes in year i respectively.

The final risk model for lung cancer death for each subject in each year is as follows:

$$
\begin{aligned}
logit(cancer) \\
&= \beta_1 age + \beta_2 age^2 + \beta_3 age^2 \mathbb{1}_{age>65} + \beta_4 age^2 \mathbb{1}_{age>70} \\
&+ \beta_5 (year\ of\ hire - 1960)^2 + \beta_6 cumulative\ exposure_{lag\ 10} \\
&+ \beta_7 \left(cumulative\ exposure_{lag\ 10}\right)^2 + \beta_8 \mathbb{1}_{active\ employment} \\
&+ \beta_9 \mathbb{1}_{active\ employment_{lag\ 1}} + \beta_{10} employment\ duration \\
&+ intercept
\end{aligned}
$$

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with the β coefficients of each variable calculated for the entire cohort of four countries.

Table S1 confirms that the selected model simulates well the natural course in the joint cohort.

The cumulative exposure variable Lag10 is the lagged cumulative exposure of 10 years. The application of lag on the cumulative exposure variable consists of introducing a lag time between exposure and cancer occurrence when modeling the relationship between the two. In practice, this involves deducting from the cumulative exposure variable the annual exposures over the last 10 years preceding the occurrence of cancer. The 10-year value is used by convention for solid cancers, although it is possible to derive other, more specific values for a given cancer by modelling.

Accepted manuscript

Table S1. Observed and simulated cumulative deaths due to lung cancer by attained age

Age (years)	Number of observed death	Number of deaths (associated 95-% confidence interval) estimated by baseline model	
50	9	10	(8-12)
60	43	44	(40-49)
70	99	113	(105-120)
80	138	139	(133-146)
90	139	140	(133-146)

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Table S2. Characteristics of the cohort of male titanium dioxide workers

Characteristics	*N (%)*
Number of workers	7341 (100)
Number of workers exposed to TiO_2	6019 (82.0)
Vital status at the end of follow-up	
Alive	5945 (81.0)
Deceased	1223 (16.7)
From lung cancer	139 (11.4)
From unknown cause	13 (1.1)
Lost to follow-up	173 (2.4)
Number of person-years	179040 (100)
Characteristics	*Mean (Standard deviation)*
Attained age at hire (years)	28.5 (9.2)
Attained age at start of follow-up (years)	30.2 (9.3)
Attained age at end of follow-up (years)	52.1 (10.9)
Employment duration (years)	13.6 (10.1)
Exposure to TiO_2 (respiratory fraction)*	*Mean (Standard deviation) [Min-Max]*
Cumulative (mg/m^3-years)	6.17 (10.47) [0.0003-142.8]
Annual average (mg/m^3)	0.47 (0.79) [0.00001-8.0]

*Exposure concentration among exposed workers

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