Cancer Epidemiology 39 (2015) 48–54

Contents lists available at ScienceDirect

Cancer Epidemiology

The International Journal of Cancer Epidemiology, Detection, and Prevention

journal homepage: www.cancerepidemiology.net

Thyroid cancer incidence around the Belgian nuclear sites: Surrogate exposure modelling

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ARTICLE INFO

Article history:
Received 8 May 2014
Received in revised form 2 October 2014
Accepted 28 October 2014
Available online 7 November 2014

Keywords:
Thyroid cancer
Nuclear sites
Surrogate-exposure modelling
Residential proximity
Prevailing wind directions
Radioactive discharge simulations

ABSTRACT

Background: In a recent ecological study among residents living around Belgian nuclear sites (the NUCABEL study), significant increased incidences of thyroid cancer were observed around the two nuclear facilities with industrial and research activities (Mol-Dessel and Fleurus), prompting further research.

Methods: The data from the NUCABEL study were reanalysed to test the hypothesis of a gradient in cancer incidence with increasing levels of exposure from these sites using three measures of surrogate exposure, being (i) residential proximity, (ii) prevailing wind directions and (iii) simulated dispersion of radioactive discharges. Single-site focussed hypothesis tests were complemented with Generalized Additive Models to estimate the exposure-response relationships.

Results: For Mol-Dessel, the results of the focussed hypothesis tests were far from significant. For Fleurus, the p-values were much closer to significance with $p = 0.05$ for Bithell's Linear Risk Score using radioactive discharge estimates as surrogate.

Conclusions: The re-analyses refute an association with the nuclear facilities for the site of Mol-Dessel. For the site of Fleurus, one of Europe's major production sites of radio-iodines, the results were less conclusive and further research suggests itself.

1. Introduction

Since the first reports on childhood leukemia clusters around nuclear power plants (NPPs) in the 1980s [1–5], controversy exists regarding the link between health risks and proximity to nuclear installations. With the publication of the German KIKK study at the end of 2007, a large-scale case-control study reporting a 1.6-fold increase [lower one-sided 95%CI: 1.26] in solid cancers and a 2.2-fold increase [lower one-sided 95%CI: 1.51] in leukemia among children living within 5 km of all German NPPs [6–9], the public health concern about nuclear activities was anew at the centre of attention. It continued to be a public health polemic in Europe with the publications of the French [10] and British [11] case-control study.

The French case-control study [10] reported an odds ratio (OR) of 1.9 (95% CI: 1.0–3.3) for acute leukemia among children (<5yrs) living within 5 km of one the 19 French NPPs. On the other hand, the British study [11]) obtained a negative estimated risk of childhood (<5yrs) leukemia and non-Hodgkin lymphoma associated with residential proximity to a NPP at birth (OR = 0.86, 95% CI 0.49–1.52).

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http://dx.doi.org/10.1016/j.canep.2014.10.011
1877-7821/

In Belgium, the public concern was boosted by the 2008 incident at the Institute for Radio-elements in Fleurus, one of Europe's major production sites of radio-iodines. During the incident (INES-rating: 3), an estimated gaseous amount of 48GBq of I-131 was released to the environment [12]. The post-incident investigation indicated points of serious concern with regard to both the operational safety and the management of the Fleurus' site [12,13] and hence, earlier exposures cannot be ruled out. In response to the incident at Fleurus, the Belgian Minister of Social Affairs and Public Health commissioned a national epidemiological study to explore health risks associated with living in the vicinity of nuclear sites. The nuclear sites under study were the four Belgian facilities with the highest radiological risk (e.g. Mol-Dessel, Fleurus, Doel, Tihange) and the French NPP of Chooz, which is close to the Belgian border. To react promptly, a multi-disciplinary research group decided that an exploratory ecological study using readily available data sources should be conducted focussing on childhood leukemia and thyroid cancer. Leukemia is the typical health outcome for studies on health risks among residents living close to nuclear sites [14]. Nevertheless, thyroid cancer is a health outcome of interest as well, known to occur after exposure to radioactive isotopes of iodine [15,16], although latency times are generally long [17]. As a result, the current study allows investigating the potential health effects of (possibly undetected and unreported) past exposures, but not of the 2008 Fleurus incident itself.

The NUCABEL study was carried out by the Belgian Scientific Institute of Public Health, the Federal Agency for Nuclear Control (FANC) and the Belgian Cancer Registry (BCR). Earlier findings [13] indicated significantly increased incidences of thyroid cancer among residents living in the 20 km proximity area around the two Belgian sites with nuclear research- and industrial activities, (i.e. Mol-Dessel and Fleurus), whereas no increased risks were found around the NPPs of Doel, Tihange, or the Belgian territory around the French NPP of Chooz. In the 20 km proximity areas of Mol-Dessel and Fleurus, incidence rate ratios (RR) of 1.19 (95%CI: 1.02–1.38) and 1.17 (95%CI: 1.04–1.33), respectively, were observed. To investigate whether there may be an association between thyroid cancer incidence and the nuclear sites, supplementary analyses were commissioned for the sites of Mol-Dessel and Fleurus. First, the hypothesis of a gradient in cancer incidence with increasing levels of exposure was tested using three measures of surrogate exposure, i.e. (i) residential proximity, (ii) prevailing wind directions and (iii) simulated dispersion of radioactive discharges. Second, the hypothesis tests were complemented with the estimation of the exposure-response relationships. The results of childhood leukaemia of the NUCABEL study are described in [18].

2. Materials and methods

2.1. Data

Thyroid cancer incidence data by commune, age and sex were received from the Belgian Cancer Registry. Data were available for the incidence years 2000–08 for the Flemish Region and for the diagnosis years 2004–08 for the Walloon and Brussels-Capital Region. In 2008, 754 people were diagnosed with thyroid cancer in Belgium. Of them, 546 were women and 208 were men, making it the 13th most common cancer among women, even though uncommon among men [19]. Thyroid cancer incidence statistics by age, sex, time and geographical location are given in [13].

Population data were obtained from the Belgian Directorate-general Statistics and Economic Information for every year from 2000 to 2008. For each year, population counts stratified by commune, 5-year age groups and sex were obtained for January 1st. In 2008, Belgium had a population of 10,666,866 inhabitants, divided over the Flemish (6,161,600), Walloon (3,456,775) and Brussels-Capital Region (1,048,491). The smallest administrative level at which age- and sex-specific data are available at the moment in Belgium are the communes. Belgium counts a total of 589 communes with a median surface of 51.8 km^2, divided over the Flemish ($n = 308$), Walloon ($n = 262$) and Brussels-Capital Region ($n = 19$) (see Fig. 1).

2.2. Nuclear sites

The nuclear sites of Mol-Dessel and Fleurus are nuclear facilities classified in Class 1 (highest radiological risk category according to

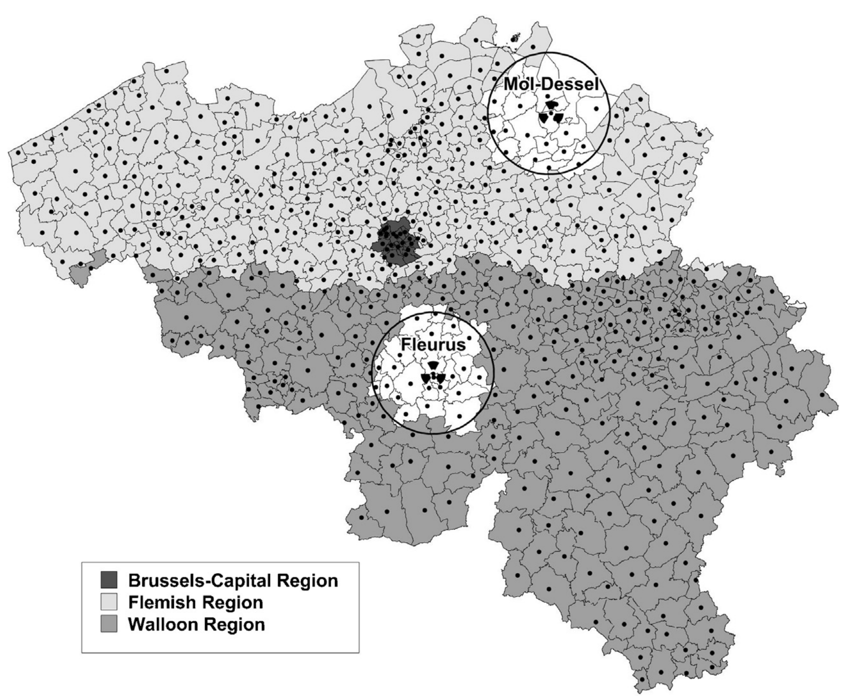


Fig. 1. Map of Belgium indicating three regions, 589 municipal communes with their centroids and the location of the site of Mol-Dessel and Fleurus, with their 20 km proximity regions.

the Royal Decree of July 20, 2001) [20], with Mol-Dessel located within the Flemish region of Belgium and Fleurus within the Walloon region. Both sites are a potential source of radioactive iodine isotopes. Several facilities in nuclear research and nuclear industry are situated on the sites (Table 1). The nuclear site of Mol-Dessel primarily consists of the Belgian Nuclear Research Centre (SCK-CEN), the Class I operator with the highest potential source term at the site. The nuclear site of Fleurus primarily consists of the Institute for Radioelements (IRE), one of Europe's major production sites of radio-iodines for commercial use. Both sites are still in activity (Table 1). In line with the literature, the proximity area of a nuclear site was defined as the area covered by all communes of which the centroid lies within the circle with a 20 km radius around the site. The locations of the sites were determined by geo-locating the reactor buildings [18].

2.3. Surrogate exposure

Three different measures of surrogate exposure to radionuclide gaseous discharges were used, i.e. (i) residential proximity to the nuclear site, (ii) prevailing wind directions and (iii) simulated radioactive discharges based on mathematical modelling. The levels of surrogate exposure were determined at commune level for all communes within the proximity area. In particular, residential proximity was calculated as the distance between the location (in Lambert 1972 coordinates) of the nuclear sites and the communes' centroids. To calculate prevailing wind directions, data on wind direction and–velocity from 2003–08 were used as collected by survey stations around the nuclear sites. Measurements were discarded when the wind velocity was below 0.2 m/s because low wind velocity is associated with unstable and continuously changing wind directions. The measurements above 0.2 m/s were used to calculate 16-sector compass roses. For every commune's centroid, the frequency (in %) of the wind blowing from the site towards the commune was then calculated. Finally, simulated radioactive discharges from the nuclear plants based on mathematical dispersion modelling were calculated. More specifically, I-131 discharges were simulated because both sites are potential sources of radioactive isotopes of iodine. This is particularly true for the site of Fleurus, which is one of the major production sites of commercially available radio-iodines in Europe. The exposures were simulated using Hotspot [21], providing analytical solutions to the transport and diffusion equations for short duration (puffs) or continuous (plumes) releases of

Table 1
Description of the nuclear sites Fleurus and Mol-Dessel, Belgium.

		Main activity	Reactors	Max. power	Period of operation	Specifications
Fleurus						
	IRE[a]	Production of radionuclides for medicine and industry			1971-	Mo-99, I-131, (Xe-133)
	Sterigenics	Sterilization of medical equipment and irradiation of foodstuffs			1978	Co-60
	NIRAS	Clean-up of former Best Medical Belgium (BMB) plant: production of radionuclides for medical applications from 1971–2012 (first IRE, then MSD-Nordion, then BMB)			2012-	2 cyclotrons and radionuclide production labs (out of operation)
	NTP	Production of Ir-192 sources for industry			1971-	Ir-192-
	IBA Pharma	Production of Pd-103 for medical applications			2002–2004	Pd-103 by cyclotron
Mol-Dessel						
	Belgoprocess	Operational waste Management			site1: 1984- site2: 1989-	ex-Eurochemic plant (1966) ex-SCK plant (1956)
	SCK-CEN[a]	Scientific and technological research (4 reactors)	BR1[b]	4 MWth	1956-	Air-cooled, graphite
			BR2[b]	120 Mwth	1963-	Research reactor
			BR3[b]	10.5 MWe dismantled	1962–1987	PWR-dismantled,
			VENUS[b]	zero power critical assembly	1964-	Experimental reactor, zero-power critical facility
		Belgian Underground Research Laboratory			1983	Study of storage conditions of radioactive waste in deep geological formations
		Laboratoria			1960	High and middle radioactivity laboratoria, mainly for nuclear fuel research
	IRRM[a]	Metrology and applied research			1960-	Laboratories, particle accelerators
	Belgonucléaire	Production of MOX[b] fuel for nuclear power plants			1973–2006	Under dismantling
	FBFC[a]-international	Production of fuel assemblies for PWRs[b] based on UO2 and MOX[b] fuels			1963-	

[a] IRE = Institute for Radio-Elements; SCK-CEN = Belgian Nuclear Research Centre; IRRM = Institute for Reference Materials and Measurements; FBFC = Franco-Belge de Fabrication Combustible.
[b] PWR = Pressurized-water reactor; BR = Belgian Reactor; VENUS = Vulcan Experimental Nuclear Study; HADES = High Activity Disposal Experimental Site; MOX = Mixed Oxides.
MWe: Megawatt electric; electric output of a power plant in megawatt, MWth: Megawatt thermal; overall power of a nuclear reactor in megawatt.

atmospheric pollutants. The model assumes that dispersion in the upwind and cross-wind direction takes the form of a Gaussian curve, with the maximum concentration in the centre of the plume. The model further assumes that a steady state exists regarding the radioactive discharges and the meteorological conditions. Calculations were carried out for standard releases (total activity: 10^{15} Bq), assuming average meteorological conditions (wind speed: 3 m/s; annual percentage rain fall: 5%) and site-specific effective release heights (Fleurus: 35 m; Mol-Dessel: 80 m). The simulated exposures were first expressed as a function of distance from the source. By multiplying these simulations by the wind direction frequencies (in %), the final exposure simulations at every commune's centroid were obtained.

2.4. Statistical methods

Single-site analyses were carried out to test the hypotheses of increasing thyroid cancer incidence with increasing levels of surrogate exposure by means of two focussed hypothesis tests, i.e. the conditional form of Stone's Likelihood ratio test [22] and Bithell's Linear Risk Score (LRS) test [23]. The advantage of Stone's test is that it is invariant to monotonic transformations of the exposure variable and as such, avoids the need to specify the exposure-response relationship. For the Bithell's Linear Risk Score (LRS) tests, scores θ_i are to be defined by the user as a function of exposure w_i. These tests are, compared to Stone's test, more powerful in case the scores properly reflect the 'exposure' effect, but assumptions are (implicitly) made regarding the scale of the 'exposure' effect when defining the scores θ_i. For the current analyses, three different types of focussed hypothesis tests were carried out: (a) the conditional form of Stone's test using the inverse residential distance from nuclear site, prevailing winds and estimated discharges as surrogates of exposure, (b) Bithell's LRS test with these surrogates of exposure as scores θ_i, and (c) Bithell's LRS test with corresponding ranks. P-values were obtained by Monte Carlo simulation from the multinomial distribution with R=5000 iterations.

To complement the focussed hypothesis tests, Generalized Additive Models (GAMs) [24], which are an extension of the Generalized Linear Models (GLMs) [25], were used to estimate the shape of the exposure-response relationships. A GLM, of which Poisson regression is a special case, relates a univariate response variable to a linear combination of predictor variables, whereas a GAM relates a univariate response to unknown smooth functions of some predictor variables. As such, the generality of a GLM is kept, but the polynomial structure of the additive effects is relaxed. To explain, let us first revisit the Poisson regression model used in [13]. The model uses the quasi-likelihood approach with Pearson-based overdispersion parameter φ to compare cancer incidences between areas while accounting for several covariates. Let Y_{ij} denote the observed number of disease cases within area $\_i$, with $i = 1, 2, \ldots, I$, and within age-sex specific stratum $\_j$, with $j = 1, 2, \ldots, J$. Further, let $\lambda_{ij} = E(Y_{ij})$ denote the expected number of disease cases being modelled using Poisson regression as

$$
\begin{aligned}
&Y_{ij} \sim Poisson(\lambda_{ij}) \\
&\log(\lambda_{ij}) = \log(n_{ij}) + \sum_{k=1}^{p} \beta_k X_{kij} = \log(n_{ij}) + \eta_{ij},
\end{aligned}
\tag{1}
$$

with the annual population size in stratum $\_j$ of area $\_i$ as offset term n_{ij} and with linear predictor

$$
\begin{aligned}
\eta_{ij} = {} & \beta_0 + \beta_1\, prox_{ij} + \beta_2 sex_{ij} + \beta_3 age_{ij} + \beta_4 age_{ij}^2 + \beta_5 (age \times sex)_{ij} \\
& + \beta_6 reg_{ij} + \beta_7 year_{ij} + \beta_8 (reg \times year)_{ij}
\end{aligned}
$$

being a function of residential proximity to a nuclear site (i.e. living or not living within the 20 km proximity area), sex, 5-year age groups, region (i.e. Flemish Region versus Walloon/Brussels-Capital Region) and diagnosis year. By exponentiation of the parameters β associated with the binary risk factors, Rate Ratios (RRs) are obtained.

When relaxing the assumption of a constant Rate Ratio for living in the proximity area of a nuclear site versus not living in the proximity area, the GLM given above in Eq. (1) gives rise to the following GAM

$$
\begin{aligned}
&Y_{ij} \sim Poisson(\lambda_{ij}) \\
&\log(\lambda_{ij}) = \log(n_{ij}) + f(W_{ij}) + \sum_{k=2}^{p} \beta_k X_{kij} = \log(n_{ij}) + \eta'_{ij},
\end{aligned}
\tag{2}
$$

with the previously assumed constant effect β_1 being now assumed to be a smooth function $f(.)$ of surrogate exposure $\underline{W}$, implying that the RR is no longer assumed to be constant, but allowed to vary smoothly as a function of exposure. The smooth function $f(.)$ is taken to be a P-splines function [26], being a function of an excessive number of equally spaced univariate B-splines [27] and an additional discrete smoothness penalty to correct for overfitting. In particular, a B-splines basis of 10 B-splines of third degree and second order smoothness penalty were used. The smoothness parameter was optimally chosen from the grid $\Lambda = 10^5$ with $p = \{-3, -2, -1, 0, 1, 2, 3, 4, 5\}$ using the Quasi-likelihood Information Criterion (QIC) [25].

3. Results

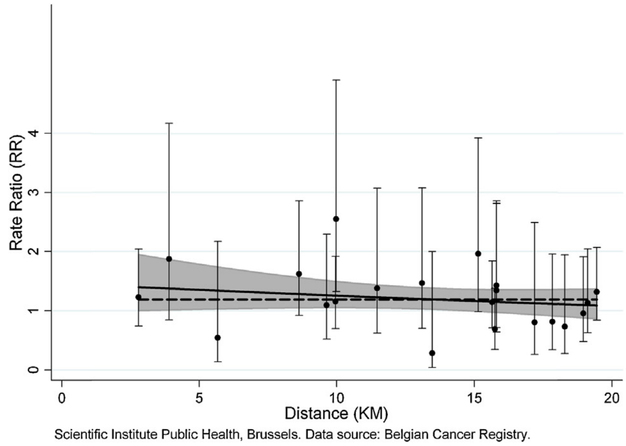
Based on the constant Rate Ratio model (Table 2), significantly increased thyroid cancer incidences were observed around the nuclear sites of Mol-Dessel and Fleurus. The focussed hypothesis tests did not yield significant results. For Mol-Dessel, all p-values were far from significance. For Fleurus, the p-values were close to significance when prevailing winds and radioactive discharge estimates were used as surrogates.

For the site of Mol-Dessel (Fig. 2), the estimated exposure-response curves using residential proximity indicated a (non-significant) positive gradient of thyroid cancer incidence. The estimated exposure–response curve based on wind direction did not suggest a gradient. The estimated exposure–response curve based on mathematical modelling of I-131 exposure suggested a

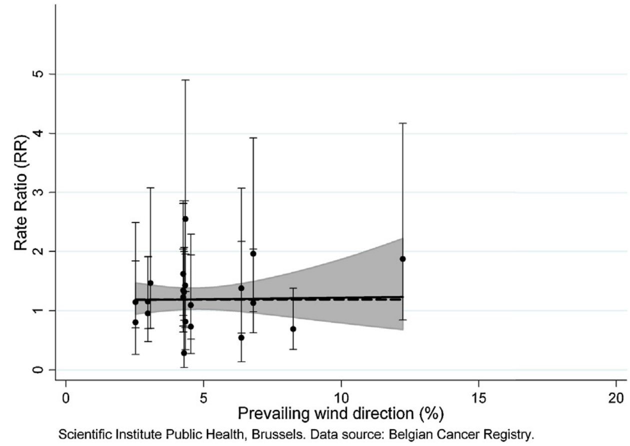
Table 2
Estimates (and 95% CI) of the constant Rate Ratio of living versus not living in the vicinity ($\leq$20 km circle) of the nuclear site and the results (p-values) of Stone's test, Bithell's Linear Risk Score test (LRS) and Bithell's Linear Risk Score test with corresponding ranks (LRS^2) for the different measures of surrogate exposure, i.e. (1) residential proximity to nuclear site, (2) prevailing winds and (3) radioactive discharge estimates based on mathematical modelling.

	Rate ratio[a]			Proximity			Wind			I-131	
	Est.	95% CI	Stone	LRS	LRS^2	Stone	LRS	LRS^2	Stone	LRS	LRS^2
Fleurus	1.17[b]	[1.04;1.33]	.50	.36	.33	.09	.09	.27	.10	.18	.05
Mol-Dessel	1.19[b]	[1.02;1.38]	.35	.18	.19	.51	.43	.43	.42	.20	.21

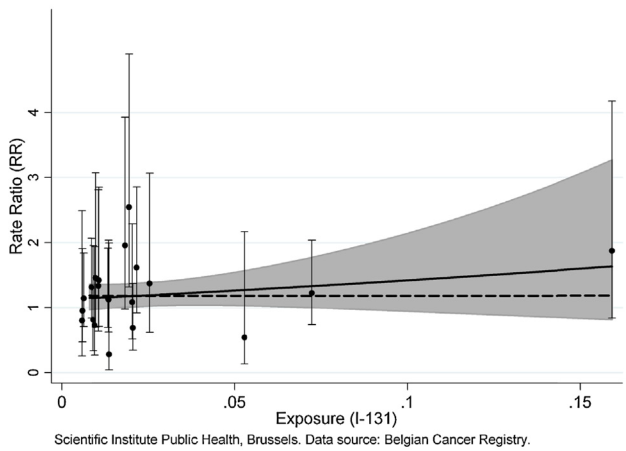
[a] Constant Rate Ratio is given by exp(β_1) within the Poisson regression model given in Eq. (1).
[b] Significant at α = 0.05



(a) Proximity



(b) Wind



(c) I-131

Fig. 2. Mol-Dessel: Rate Ratios (RRs) and 95% CI (gray area) of thyroid cancer incidence within the 20 km proximity area as a smooth function of (a) residential proximity to the nuclear site,(b) prevailing wind directions and (c) simulated I-131 discharges. The horizontal dashed line represent the constant RR. The dots represent the commune-specific RRs and the corresponding 95% CIs are represented by the lines
* Data source: Belgian Cancer Registry.

(non-significant) positive gradient of thyroid cancer incidence as well, although driven by one commune (Dessel commune-specific RR = 1.87; 95%CI = [0.84;4.17]).

For the site of Fleurus, the estimated exposure-response curve did not show any evidence for a gradient in thyroid cancer incidence with decreasing distance (Fig. 3). The exposure–response relationship as a function of wind direction suggested a gradient in thyroid cancer incidence. However, this was not confirmed by the focussed hypothesis tests. The discharge based exposure–response relationship showed an increase at the lower exposure levels, but a drop at the highest levels. This drop was driven by the commune of Fleurus (commune-specific RR = 0.86; 95%CI = [0.45;3.19]). These findings were consistent with the results from the focussed hypothesis tests. Only Bithell's LRS test based on ranks yielded significant results because it is, compared to Stone's test, the most powerful test to detect linearity and is, compared to Bithell's LRS test based on exposure levels, the most robust to outliers in the exposure variable, and hence, the least influenced by the 'outlying' result from the commune of Fleurus.

4. Discussion

The objective of the current study was to further examine the earlier positive findings from the NUCABEL study [13], indicating significantly increased incidences of thyroid cancer around the two Belgian nuclear sites with industrial and research activities, i.e. Mol-Dessel and Fleurus. In particular, the hypothesis of a gradient in cancer incidence with increasing levels of radiation exposure from these sites was investigated. However, these levels are often below the detection limit of the routine environmental monitoring in Belgium, by which background radiation is predominantly measured. Therefore, the radiological discharges from the sites, in particular the gaseous discharges, were considered. Unfortunately, the non-aggregated measurements are not publicly available, necessitating the use of surrogates.

Three different surrogates of radiological gaseous exposure were employed; (i) residential proximity, (ii) prevailing wind directions, and (iii) simulated radioactive exposure based on mathematical dispersion modelling of the discharges. Each measurement has its pro's and con's. The use of residential proximity as surrogate exposure assumes an isotropic and isotonic decrease of exposure with distance. However, although commonly used [28,29], this approach ignores among others the impact of wind direction and is therefore radio-ecologically not plausible [30]. The same holds true when using prevailing wind directions as surrogate of exposure, by which the impact of distance is ignored. The radio-ecologically most plausible surrogates of exposure are the ones using radioactive exposure

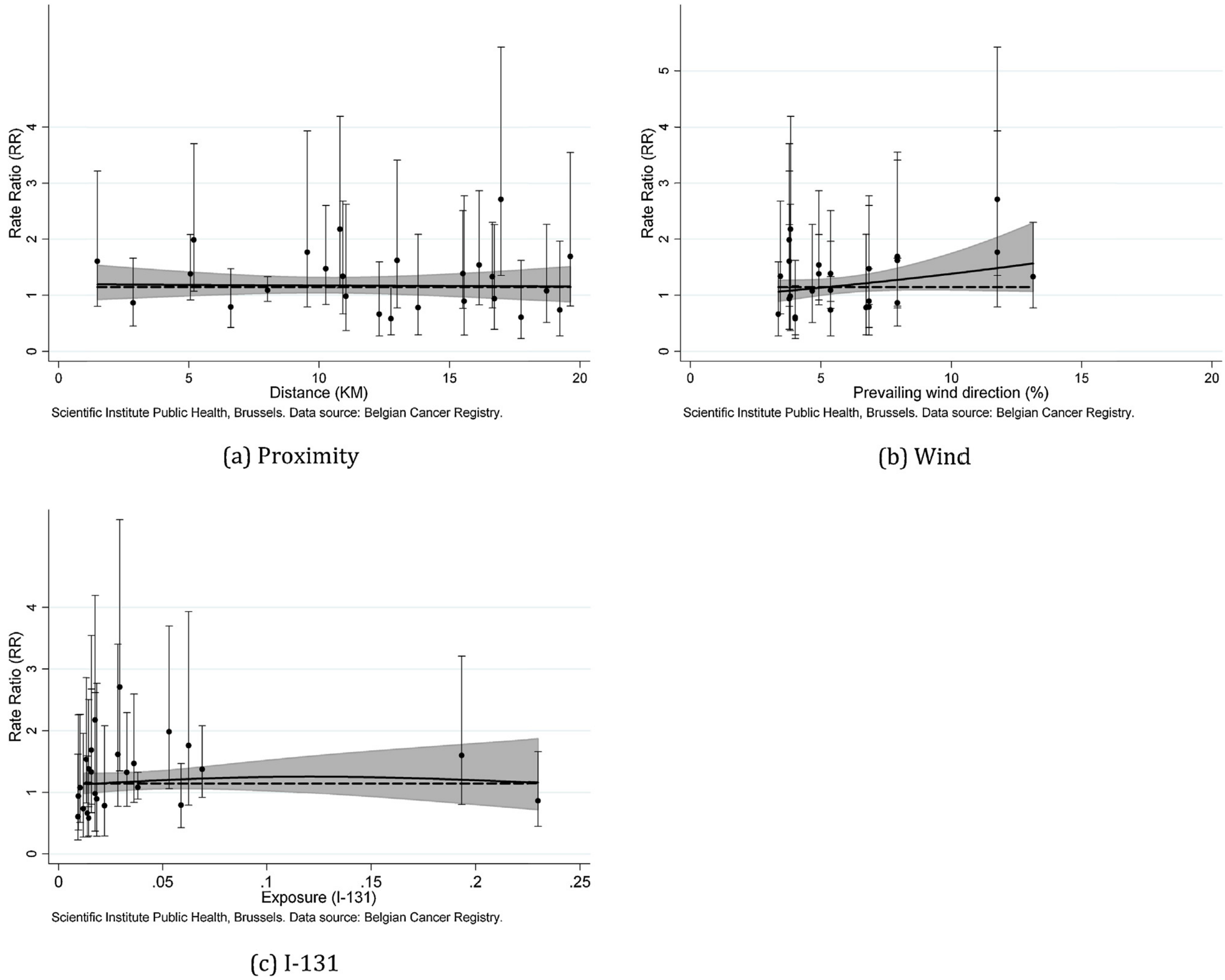


Fig. 3. Fleurus: Rate Ratios (RRs) and 95% CI (gray area) of thyroid cancer incidence within the 20 km proximity area as a smooth function of (a) residential proximity to the nuclear site,(b) prevailing wind directions and (c) simulated I-131 discharges. The horizontal dashed line represent the constant RR. The dots represent the commune-specific RRs and the corresponding 95% CIs are represented by the lines
* Data source: Belgian Cancer Registry.

simulations based on mathematical dispersion modelling, as they take into account the combined effects of distance and wind direction as well as the physical characteristics of radionuclide dispersion. However, this last surrogate is the most prone to misclassification errors as it combines (the misclassification errors of) distance and wind direction. Finally, note that more detailed radionuclide dispersions models exist [31,32]. However, such detailed dispersion models would be off-balance with the size of the geographical unit of analysis (communes' level) used in the current study.

In addition to the different surrogates of exposure, different statistical methods were exploited. In particular, three different focused hypothesis tests (i.e. Stone's test, Bithell's LRS test with levels of surrogate exposure and Bithell's LRS test with ranks) were used, all ranging differently with respect to the trade-off between power and the need to correctly specify the exposure–response relationship. Finally, to complement the focused hypothesis tests, the exposure–response relationships were estimated using GAMs allowing the Rate Ratio for living versus not living in the proximity area of a nuclear site to vary smoothly as a function of exposure. To our knowledge, this is the first use of this type of models within the context of point-source exposure modeling. This approach of estimating the exposure-response relationship using GAMs is an extension of the Poisson regression model, the use of which has been advocated within this context [8,28].

The use of different statistical methods and measures of surrogate exposure has an important added value. Since every method and every surrogate of exposure inherently relies on some assumptions, the use of multiple methods/surrogates of exposure reduces the dependence of the (combined) results on the assumptions and provides nuanced and complementary insights. Consistent results strengthen the confidence of a result to be "true" as opposed to a "spurious" result driven by assumptions.

The results from the multiple methods/measures of exposure approach should be regarded in the light of the ecological design of the study and its drawbacks. The ecological design entails that population-level data are compared rather than individual-level data. The most pertinent drawbacks of the ecological design include the ecological bias (i.e. associations at population-level do not necessarily reflect associations at individual-level) and the failure to account for important (individual-level) variables. For example, the current study does not account for individual migration patterns, resulting in exposure misclassification. Another important source of exposure misclassification is the size of the geographical areas that correspond to the smallest administrative level for which health data are (currently) available in Belgium (i.e. commune level). Such exposure misclassification, even when non-differential, may lead to spurious positive or negative results [33–35]. For all these reasons, the evidence from ecological studies is generally considered as weaker when compared to e.g. well-conducted (large scale) case-control studies [28], which are more resource- and time intensive compared to ecological studies. A way to enhance statistical power, is by conducting multi-site analysis by grouping nuclear sites. However, we opted not to do so because the sites of Mol-Dessel and Fleurus are characterized by different types of nuclear activities.

The NUCABEL study did not allow investigating the health effects of the Fleurus 2008 incident itself as a result of the ecological design used and the time period of the available cancer incidence data (2000/2004-2008). Instead it allowed investigating the potential health effects of (possibly undetected or unreported) past exposures. As the timing of such possible past exposures is unknown, the cross-section over all ages was taken. The two main pathways of exposure from release of radionuclides in the atmosphere by nuclear installations are gamma radiation and ingestion of radionuclides through food contamination. Because the ecologic design was used, only the first pathway could be taken into account. However, food contamination is generally not considered a geographical risk factor in Belgium as a result of the Belgian open food economy.

Taking all these considerations into account, we conclude that the surrogate-exposure analyses refute the earlier positive finding for the site of Mol-Dessel. For the site of Fleurus, the results were less conclusive. The inconclusive results for the site of Fleurus, one of the major production sites of radioiodines in Europe, ask for further research. We recommended preparing cancer data at smaller geographical level. These data are expected to be available in the near future, and will allow repeating the analyses with greater geographical detail and for an extended time period.

Conflict of interest

No competing financial interests exist.

Contributors

The idea and contents of the article emerged from discussions among the authors, who have experience in biostatistics, epidemiology, radiology and nuclear engineering. KB and AVN designed the study. MS obtained the results of the dispersion modelling. KB implemented the statistical analyses. All authors contributed to the discussions regarding the results of the analyses. KB wrote the first draft. All authors contributed to the subsequent revisions and approved the final version. JF, LVB and AVN were responsible for the realisation of the study in their respective institutes (BCR, FANC, and WIV-ISP). AVN coordinated the consortium.

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