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Thyroid cancer incidence near nuclear sites in Belgium: An ecological study at small geographical level

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In Belgium, variations in thyroid cancer incidence were observed around the major nuclear sites. The present ecological study investigates whether there is an excess incidence of thyroid cancer among people living in the vicinity of the four nuclear sites at the smallest Belgian geographical level. Rate ratios were obtained from a Bayesian hierarchical model for areas of varying sizes around the nuclear sites. Focused hypothesis tests and generalized additive models were performed to test the hypothesis of a gradient in thyroid cancer incidence with increasing levels of surrogate exposures. No evidence was found for more incident cases of thyroid cancer near the two nuclear power plants. Regarding the two industrial and research nuclear sites, no evidence for a higher incidence in the vicinity of Mol-Dessel was observed, whereas a slightly nonsignificant higher incidence was found in the close vicinity of Fleurus. In addition, significant gradients for thyroid cancer incidence were observed with the different types of surrogate exposure considered in the 20 km area around the site of Fleurus (decreasing distance, increasing wind direction frequency and increasing exposure to estimated hypothetical radioactive discharges of iodine-131). In the investigation at the smallest Belgian geographical level, variations in thyroid cancer incidence were found around the Belgian nuclear sites. Significant exposure–response relationships were also observed for the site of Fleurus. Further investigations into these findings could be useful to allow inferring causal relationships on the origin of variations in incidence and to provide information at the individual level.

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Abbreviations: 95% CI: 95% credibility intervals; CAR: conditional autoregressive; ESR: European Standard Rates; IMA-AIM: Intermutualistic Agency; LRS: Bithell's linear risk score; R-INLA: R-integrated nested Laplace approximations; RR: rate ratio; SIR: standardized incidence ratio
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Introduction

Exposure to ionizing radiation, particularly during childhood, is the best-established risk factor associated with thyroid cancer (mainly papillary forms).[1–3] Ionizing radiation has the capacity of damaging tissue by ionizations, which disrupt molecules directly and also produces highly reactive free radicals, which in turn can affect nearby cells. The consequence is that biological molecules suffer from local disruption, which can lead to replication and transcriptional errors and, thus, can result in premature aging and cancer.[4,5] Ionizing radiation can theoretically cause almost all forms of cancer while the bone marrow, the thyroid, the lungs and the female breasts are known to be particularly sensitive to radiation induction of cancer.[4,5]

The radionuclide iodine-131 is known to be a major contributor to thyroid cancer risk in the case of nuclear accidents.[6] Studies on survivors of the atomic bombings at Hiroshima and Nagasaki, Japan, have demonstrated significantly higher risks of developing thyroid cancer after radiation exposure during childhood.[7,8] A direct consequence of the Chernobyl disaster was an increase in the number of thyroid cancers in children during the years after the accident.[8,9] Radiation-related risk of thyroid cancer after exposure during childhood has been shown to persist for decades after exposure.[7] Exposure during adulthood has been less clearly linked

What's new?
Potential cancer risk associated with living near nuclear installations has long been a public concern. In Belgium, a previous study found a higher incidence around the two nuclear sites with research and industrial activities, but not around the two nuclear power plants. Exposure misclassification due to the large geographical scale could not be excluded, however. The present study, which uses data available at the smallest Belgian geographical level, confirms the previously-described incidence patterns around the nuclear power plants and for one of the research and industrial sites. There was a significant exposure-response relationship for the latter. This finding is valuable for thyroid cancer etiology.

to thyroid cancer; ionizing radiation can also cause thyroid cancer in adults, but they will occur after exposure to higher doses.[10–12]

In Belgium, a radiological incident happened in 2008 at the Institute for Radio-Elements situated in the nuclear site of Fleurus. At the same time, the German KiKK-study (Kinderkrebs in der Umgebung von Kernkraftwerken) on childhood cancer, more specifically childhood leukemia, boosted the public concern about the possible health risks associated with living in the vicinity of nuclear power plants worldwide.[13,14] In response, the Belgian Minister of Social Affairs and Public Health commissioned a study to assess the possible health risks for populations living in the proximity of nuclear power plants or other facilities that can be at the origin of a release of radioactive material. The results of this ecological study, performed at the level of the communes (municipalities), showed no higher incidence of thyroid cancer around the two Belgian nuclear power plants. For the two nuclear sites with research and industrial activities, a slightly higher incidence of thyroid cancer was observed compared to the regional average.[15–18]

The present study is the follow-up thereof and follows the recommendation to make data available at smaller geographical level. The present study was performed at the level of the statistical sectors, a subdivision of commune. The statistical sector, which was defined by the Belgian statistical office based on social, economic and urban characteristics, is the smallest area in Belgium. Such data has the advantage of reducing the risk of misclassification of the exposure and ecological bias thanks to a smaller within-area variation of the exposure.[19–21] More specifically, the study has investigated whether thyroid cancer incidence is higher than expected in the vicinity of the Belgian nuclear sites. In a second phase, the study investigated whether there is evidence for a gradient in cancer incidence with increasing surrogate exposures from nuclear sites.

Materials and Methods

Population and cancer data

Population data were collected by the Intermutualistic Agency (IMA-AIM) which gathers demographic and socioeconomic data concerning the members of the Belgian mutual insurance companies. Population counts were provided by sex, age groups (0–4 years, 5–9 years, …, 80–84 years, ≥85 years) and statistical sector for December 31 of each year. Data was reliable from 2006 onwards.

Thyroid cancer incidence data (defined by the International Classification of Diseases, 10 revision, code C73) was selected from the Belgian Cancer Registry, a national population-based registry. The incidence year, sex, age and place of residence at diagnosis were used to characterize the cancer diagnosis of people diagnosed between January 1, 2006 and December 31, 2014.

In 2014, the IMA-AIM collected information on a population of 10,841,091 people, among which 5,311,307 were male and 5,529,784 were female. The Belgian territory is divided into the Flemish (the northern part of Belgium, 6,318,580 inhabitants), Walloon (the southern part of Belgium, 3,454,499 inhabitants) and Brussels Capital (1,068,012 inhabitants) Regions. There are 19,782 statistical sectors in Belgium, as defined by the Belgian statistical office in 2011. On average, the statistical sector has a surface area of 1.5 km^2 and a population count of about 500 inhabitants ranging from 0 to 7,897 inhabitants (these latter located in the city of Brussels) in 2014. In comparison, there are 589 communes in Belgium, which have on average an area of 50 km^2 and a population count of about 18,000 inhabitants.

Nuclear sites and surrogate exposure

Nuclear sites. The nuclear sites under study are Doel (Flemish Region), Tihange (Walloon Region), Mol-Dessel (Flemish Region) and Fleurus (Walloon Region), the four Belgian nuclear sites containing facilities of class 1 defined as facilities with the highest radiological risk.[22] Doel and Tihange are electricity-generating nuclear power plants. The nuclear site of Mol-Dessel primarily consists of the Belgian Nuclear Research Centre and hosts a combination of nuclear activities (applied research and metrology, scientific and technological research, operational waste management). The nuclear site of Fleurus primarily consists of the Institute for Radio-Elements, one of the major production sites of radioiodine for use in diagnostic and therapeutic nuclear medicine in Europe (see,[17] for a more detailed description of the sites). In August 2008, an estimated activity of 48.109 Bq of iodine-131 released to the atmosphere over 4 days (International Nuclear and Radiological Event Scale, INES-rating: 3/7).

Distance and proximity areas. In the literature, a distance of 20 km is usually taken as the vicinity around the nuclear installation. We considered different proximity areas defined as a circle of 5 km radius centered on the site and ring-shaped areas until 20 km (5–10, 10–15 and 15–20 km). The proximity area around a nuclear site was constructed as the aggregation of the statistical sectors having their centroid lying within the proximity area (for more details, see Supporting Information).

Prevailing winds. From data on wind direction and speed collected between 2006 and 2014 by the Belgian Federal Agency for

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Nuclear Control, we calculated wind direction frequency for the 16 wind rose sectors around each nuclear site. The statistical sectors lying within the 20 km around each nuclear site were then categorized into one of the 16 wind rose sectors on the basis of their centroid and were attributed to the corresponding wind direction frequency (for more details, see Supporting Information).

Hypothetical radioactive discharge estimates. A modeled estimate of the direct radiological impact of hypothetical releases of radioactive gaseous substances from the nuclear plants within the 20 km around the site was used as a measure of surrogate exposure. This modeled estimate was calculated using a mathematical dispersion model (Hotspot[23]) by the Federal Agency for Nuclear Control for the sites of Mol-Dessel and Fleurus, as motivated later (Results). The hypothetical radioactive discharge estimates for each statistical sector have been calculated as the product of the percentage of time that the wind was blowing towards the statistical sector multiplied by the modeled hypothetical radioactive discharges for that statistical sector (for more details, see Supporting Information).

Statistical analyses

Descriptive analyses. The occurrence of thyroid cancer as a function of age and sex was investigated by calculating age- and sex-specific incidence rates. Regional incidences were explored by calculating the age- and sex-standardized rates (European Standard Population, 2013 edition[24]). Ninety-five percent confidence intervals were calculated by Poisson approximation.

Incidence of thyroid cancer around nuclear sites. Rate ratios (RR) in the proximity areas were estimated from a Bayesian hierarchical model[25,26] (for more details, see Supporting Information). The posterior summaries of the rates and their 95% credibility intervals (95% CI) were obtained by sampling from the posterior distribution for each statistical sector and then averaging over the proximity areas. We used the R-INLA (R-Integrated Nested Laplace Approximations) package R version 3.2.2.*

In the IMA-AIM data, the age of the population is calculated at the end of the year. Information on the statistical sector relates to the statistical sector of residence at the end of the year. For incident cases, information on the statistical sector of residence was the statistical sector where the case lives at the end of the year of diagnosis. The age was the age of the case at the time of diagnosis. This resulted in discrepancies when comparing the cases and the reference population. A sensitivity analysis was performed to have a view at the beginning of the year for the cases and the population. We calculated the age on January 1 and attributed the statistical sector of residence on December 31 of the preceding year for the cases and the population.

In addition, to interpret the signals of slightly elevated thyroid cancer incidences around the nuclear site, we also investigated whether people living near that nuclear site, are more likely to be screened prone to the detection of subclinical disease as a result of overdiagnosis. The proportion of tumors of size T1, that is, <2 cm (TNM classification) during the period 2006–2014 in the 0–5 km proximity area around the site was compared to the proportion of tumors of size T1 in the reference region using the Chi-square test for comparison of an observed and a theoretical proportion.

Finally, to investigate the thyroid cancer incidence after the Fleurus incident in 2008, standardized incidence ratios (SIR; i.e., ratio of the observed number of cases and the expected number of cases based on age, sex and yearly reference rates) were calculated for the period 2006–2007 and for the period 2008–2014 in the 20 km around Fleurus, for all ages and for ages <30 years. Thyroid cancer can develop 5 years to several decades after exposure.[2,3] Hence we also considered a 5-year latency period between the time of the incident and the time of diagnosis as it was observed after the Chernobyl accident[27,28] and calculated SIR for the years 2013–2014.

Association between surrogate exposures and incidence of thyroid cancer around nuclear sites. Surrogate exposures considered were the inverse residential distance from nuclear site, the wind direction frequency, and the hypothetical radioactive discharge estimates. To test the hypothesis of a positive gradient in thyroid cancer incidence with increasing levels of each surrogate exposure, three focused hypothesis tests were performed: (*i*) the conditional form of Stone's test;[29] (*ii*) the conditional form of Bithell's Linear Risk Score test (LRS)[30] and (*iii*) the conditional form of Bithell's LRS rank test with corresponding ranks. Monte Carlo simulations from the multinomial distribution with 5,000 iterations were performed to obtain the p values of the tests.

Finally, the shapes of the exposure–response relationships were investigated using generalized additive models.[31] In particular, a Poisson regression model was extended by allowing the RR to vary smoothly as a function of exposure (see Ref. 16 for a more detailed description of the statistical methodology). The analyses were generated using SAS software (version 9.3, SAS Institute Inc., Cary, NC) and R software version 3.2.2.

Ethical approval

As our study takes entirely place within the legal framework of the Belgian Cancer Registry, no ethical approval of concerned patients was needed (privacy law of 08/12/1992 Chapter III art 9 §2 2e a) and 2e b)[†] which refers to Health law of 2006[‡]).

*R Core Team (2016). R: A language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria. URL https://www.R-project.org/.

[†]http://www.privacycommission.be/sites/privacycommission/files/documents/CONS_wet_privacy_08_12_1992.pdf.

[‡]http://www.kankerregister.org/media/docs/Wetgeving/Staatsbladgezondheidswet13122006pub22122006.pdf.

Data availability

The data that support the findings of our study are available upon reasonable request. The data can be given within the secured environment of the Belgian Cancer Registry, according to its regulations, and only upon approval by the Information Security Committee.

Results

Descriptive analyses

Over the period 2006–2014, 7,780 cases of thyroid cancer were diagnosed in Belgium. 7,285 cases were included in the analyses. For 298 cases, the coupling of the Belgian Cancer Registry data to IMA-AIM data was not possible and thus information on the statistical sector was missing. In addition, information on the statistical sector was not valid for 197 cases. These cases were not included in the analyses.

Figure 1 shows the age- and sex-specific crude incidence rates of thyroid cancer in Belgium for the period 2006–2014. Rates were lower in children than in adults. Thyroid cancer occurred significantly more frequently among women compared to men for the ages ranging from 10 to 79 years. For female adults, the incidence rates steadily raised until the age of 55–59 years and dropped afterward. For male adults, the incidence rates also raised until the age of 65–74 years.

Supporting Information Figure S1 depicts the age- and sex-standardized rates to the European Standard Population of thyroid cancer per 100,000 person-years at risk (European Standard Rates, ESR) for the three Belgian regions separately. The ESR in the Flemish Region was significantly lower than the ESR in the

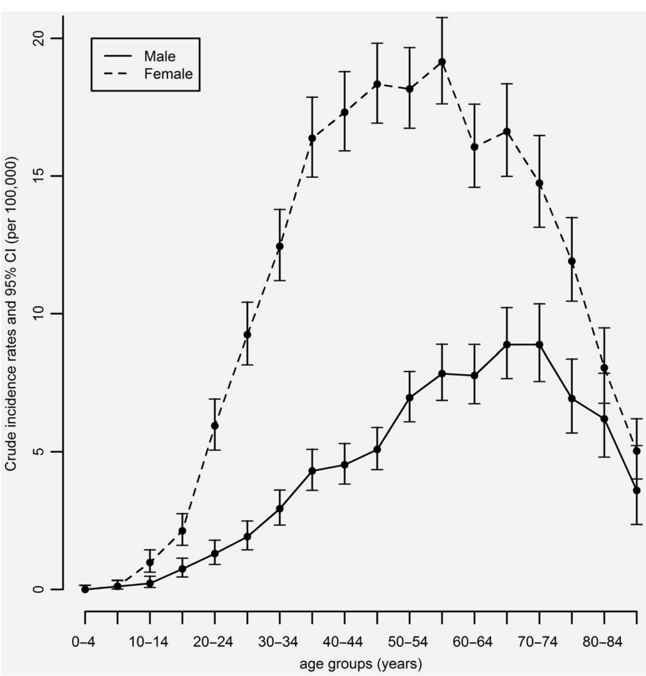

Figure 1. Age- and sex-specific incidence rates and 95% confidence intervals (95% CI) of thyroid cancer in Belgium, 2006–2014.

Table 1. Rates ratios (RR) of thyroid cancer incidence and 95% credibility intervals (CI) for the 0–5, 5–10, 10–15 and 15–20 km proximity areas around each nuclear site for the period 2006–2014, all ages

Proximity area around the nuclear site	PY	O	E	RR (95% CI)[1]
Doel				
0–5 km	31,497	<5	<5	0.78 (0.58;1.01)
5–10 km	230,629	11	13.8	0.76 (0.62;0.93)
10–15 km	1,459,668	58	89.5	0.76 (0.65;0.87)
15–20 km	4,779,764	215	274.4	0.82 (0.74;0.90)
Tihange				
0–5 km	384,433	32	40.3	0.83 (0.68;1.00)
5–10 km	309,643	24	32.5	0.84 (0.72;0.98)
10–15 km	603,513	47	63.7	0.84 (0.74;0.95)
15–20 km	1,360,054	112	143.6	0.86 (0.78;0.95)
Mol-Dessel				
0–5 km	305,918	18	18.8	1.00 (0.80;1.24)
5–10 km	625,313	45	38.2	1.00 (0.85;1.17)
10–15 km	865,085	49	52.9	0.97 (0.85;1.10)
15–20 km	1,694,147	103	102.8	0.96 (0.86;1.07)
Fleurus				
0–5 km	734,039	95	77.4	1.13 (0.99;1.30)
5–10 km	1,819,518	200	187.4	1.06 (0.96;1.16)
10–15 km	1,350,860	146	142.9	1.01 (0.92;1.10)
15–20 km	1,299,308	121	137.5	0.97 (0.89;1.06)
All sites				
0–5 km	1,455,887	146	138.3	1.00 (0.90;1.10)
5–10 km	2,985,103	280	271.9	0.98 (0.91;1.05)
10–15 km	4,279,126	300	348.9	0.91 (0.86;0.97)
15–20 km	9,133,273	551	658.4	0.90 (0.86;0.94)

Age is calculated at diagnosis for the cases, on December 31 for the population. The statistical sector corresponds to the statistical sector of residence on December 31 for the cases and the population.
[1]Rates ratios and their 95% credibility intervals.
Abbreviations: E, expected number of cases; O, observed; PY, person-years.

Table 2. Results (*p* values) of the Stone's test, the Bithell's linear risk score test (LRS) and the Bithell's linear risk score test with rank (LRS rank) for the period 2006–2014, all ages

	Doel	Tihange	Mol-Dessel	Fleurus
Distance				
Stone	0.97	0.45	0.41	<0.01
LRS	0.90	0.45	0.44	<0.01
LRS rank	0.90	0.44	0.42	<0.01
Wind direction frequency				
Stone	0.17	0.42	0.36	<0.05
LRS	0.08	0.33	0.16	<0.01
LRS rank	0.53	0.25	0.13	<0.01
Hypothetical radioactive discharge estimates				
Stone	–	–	0.30	<0.001
LRS	–	–	0.23	<0.001
LRS rank	–	–	0.27	<0.001

Walloon or in the Brussels Capital Region. Over time, incidence rates increased in the three Belgian Regions. The increase in incidence of thyroid cancer concerns the early stage, that is, Stage I.[32] More intensive use of thyroid imaging and surgery can potentially lead to more incidental thyroid cancer detection.[33]

Because of these regional differences in thyroid cancer incidence, different reference populations were used to calculate the expected number of cancer cases in the subsequent analyses. For the nuclear sites located in a Flemish commune (i.e., for Doel and Mol-Dessel), the reference was the Flemish population whereas, for the nuclear sites located in a commune of the Walloon Region (i.e., for Tihange and Fleurus), the reference was the Walloon/Brussels Capital population.

Incidence of thyroid cancer around nuclear sites

RR was obtained from a conditional autoregressive (CAR) model[26] with Poisson distribution adjusted for the region. Table 1 presents the RR and their 95% CI for the proximity areas of 0–5, 5–10, 10–15 and 15–20 km around each nuclear site. Around the nuclear sites of Doel and Tihange, lower incidences of thyroid cancer were observed. The RR was significantly lower than expected in the 5–10, 10–15 and 15–20 km. The nuclear site of Mol-Dessel showed nonsignificant RR close to one. Around the nuclear site of Fleurus a (borderline) nonsignificant higher incidence was observed in the 0–5 km proximity area, RR = 1.13 (95% CI: 0.99;1.30). Then, the RR decreased to 0.97 (95% CI: 0.89;1.06) in the 15–20 km around

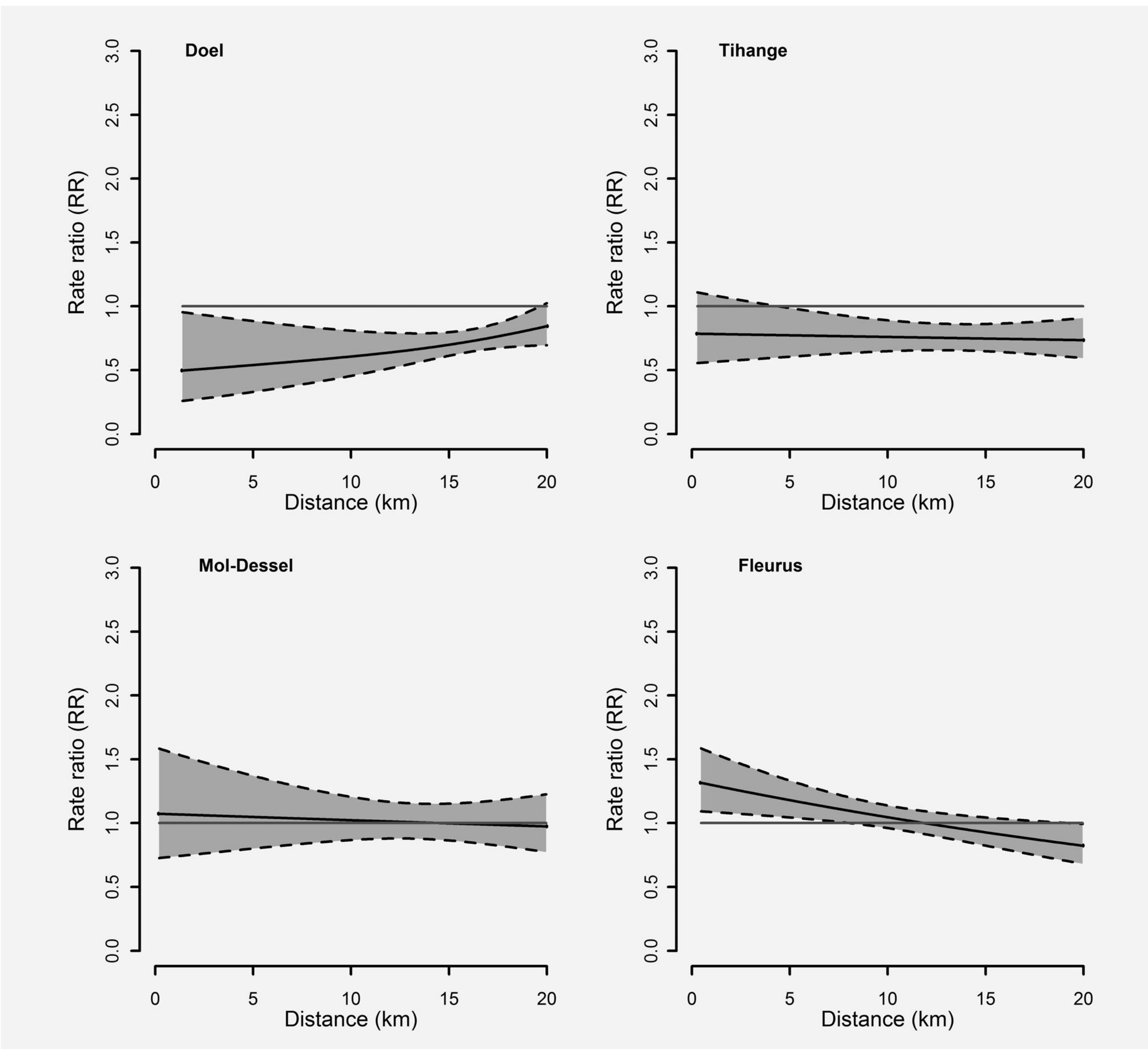

Figure 2. Rate ratios (RR) and 95% confidence intervals (dotted lines) of thyroid cancer incidence within the 20 km around the four nuclear sites as a smooth function of the distance to the site for the period 2006–2014, all ages.

the site. Considering the four Belgian sites together, the RR ranged from 1.00 (95% CI: 0.90;1.10) in the 5 km around the sites to 0.90 (95% CI: 0.86;0.94) in the 15–20 km.

Compared to the main analysis, the use of the statistical sector of the residence at the end of the year preceding the incidence year in the sensitivity analysis resulted in small changes (Supporting Information Table S1). As in the main analysis, around the nuclear sites of Doel and Tihange, lower incidences of thyroid cancer were observed. For the nuclear site of Mol-Dessel, the RR was nonsignificantly decreasing from 1.00 for the 0–5 km proximity area to 0.95 in the 15–20 km proximity area. In the 5 km around the nuclear site of Fleurus, a higher nonsignificant RR was observed (RR = 1.10, 95% CI: 0.95;1.27). For the four Belgian sites together, the results of the main and sensitivity analyses were similar.

We also investigated whether people living close to the Fleurus nuclear site were more likely to be screened, prone to the detection of subclinical diseases as a result of overdiagnosis. The observed proportions of tumors of size T1 were 62.5% in males and 76.1% in females in the 0–5 km proximity area around Fleurus. The observed proportions were not significantly different among males (Chi-square test, p-value = 0.84), neither among females (Chi-square test, p-value = 0.28) from the theoretically expected proportions of tumors of size T1 in the Walloon Region (60.0% in males and 70.1% in females).

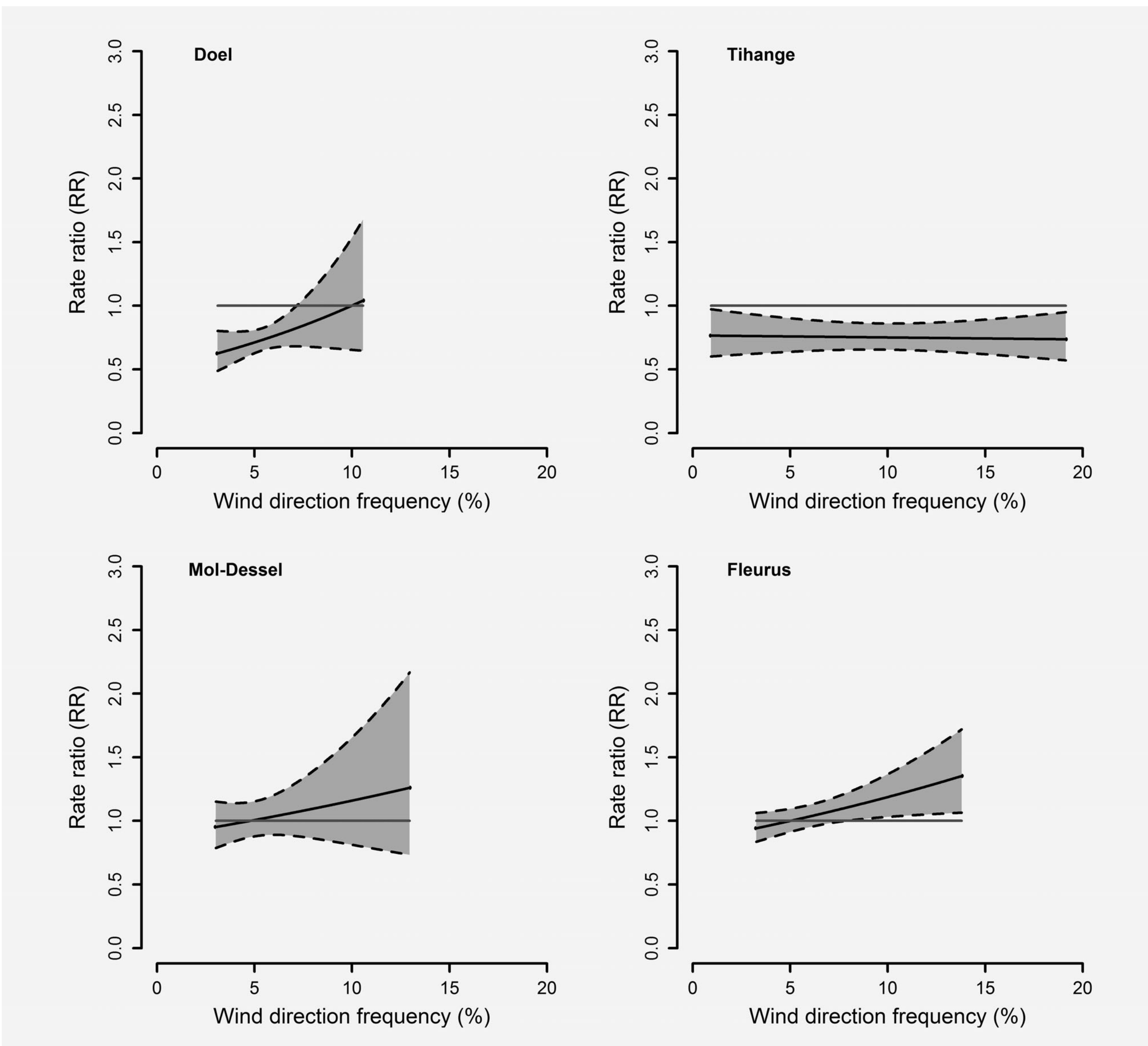

Figure 3. Rate ratios (RR) and 95% confidence intervals (dotted lines) of thyroid cancer incidence within the 20 km around the four nuclear sites as a smooth function of the wind direction frequency for the period 2006–2014, all ages.

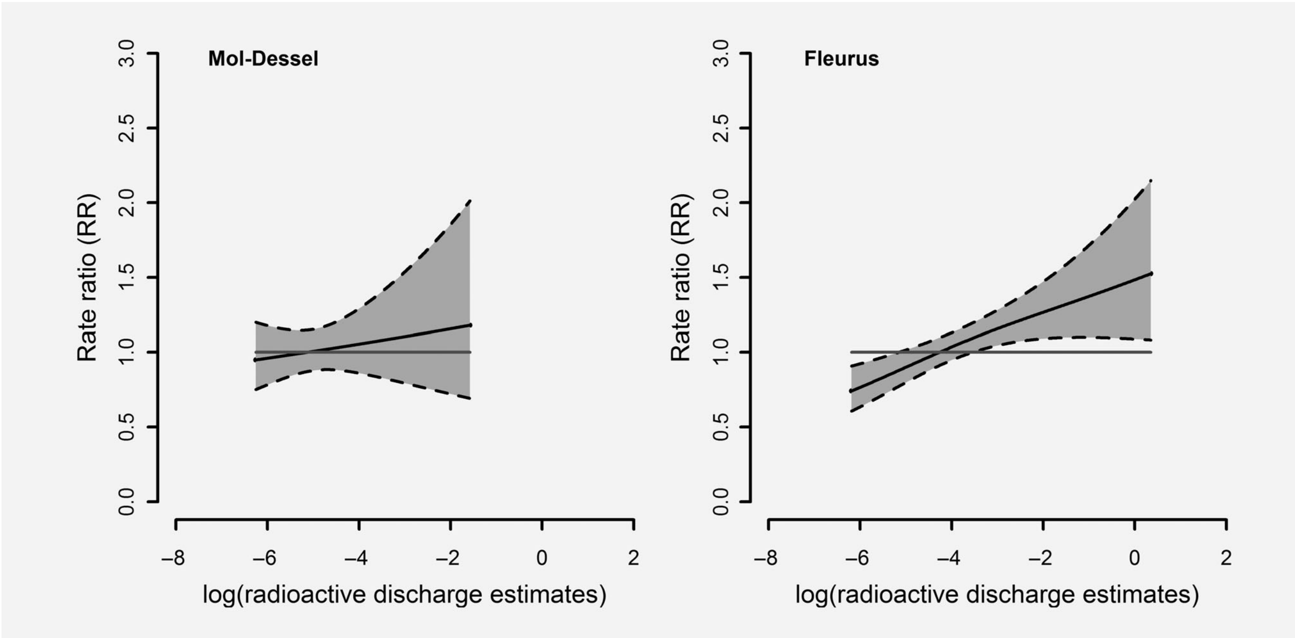

Figure 4. Rate ratios (RR) and 95% confidence intervals (dotted lines) of thyroid cancer incidence within the 20 km around the two nuclear sites as a smooth function of the logarithm of the exposure estimates resulting from hypothetical radioactive discharges (iodine-131) for the period 2006–2014, all ages.

Finally, the thyroid cancer incidence after the Fleurus incident in 2008 was compared to the incidence before the incident. For all ages, 121 and 441 cases were diagnosed over the periods 2006–2007 and 2008–2014, respectively, resulting in SIR and 95% confidence intervals of 1.20 (0.98;1.41) and 1.06 (0.96;1.16), respectively. The SIR for the period 2013–2014 was not significantly different (200 diagnosed cases, SIR = 1.07 [0.92;1.22]). For people having less than 30 years, 7 and 35 cases were diagnosed over the periods 2006–2007 and 2008–2014, resulting in SIR and 95% confidence intervals of 0.88 (0.23;1.52) and 0.98 (0.66;1.31), respectively. Fourteen cases were diagnosed over the period 2013–2014; this resulted in a SIR of 0.79 (0.37;1.20). It has to be stressed that these results, especially among people having less than 30 years of age, are based on a small number of cases.

Association between surrogate exposures and incidence of thyroid cancer around nuclear sites

Table 2 presents the results of the tests of a positive gradient in thyroid cancer incidence with increasing surrogate exposures in the 20 km around the nuclear sites. The conditional forms of Stone's test, the LRS test with inverse residential distance from the nuclear site and the LRS rank were not statistically significant for the nuclear sites of Doel, Tihange or Mol-Dessel. Figure 2 which visualizes the exposure-response curves as estimated by the spline models, that is, the RR of thyroid cancer incidence as a smooth function of distance to the nuclear site does not support the hypothesis of a decrease in thyroid cancer incidence with increasing distance for Doel, Tihange and Mol-Dessel. For Fleurus, the tests of the gradient were significant (p values <0.01) and the exposure–response curve is suggestive for a decreasing trend in thyroid cancer incidence with increasing distance.

Figure 3 visualizes the RR of thyroid cancer incidence as a smooth function of the percentage of time the wind is blowing into a particular direction. For Doel, the figure supports the hypothesis of an increase in thyroid cancer incidence with wind direction frequency. This is mostly confirmed by the LRS test (p-value = 0.08) but not by the LRS rank test (p-value = 0.53) nor the Stone's test (p-value = 0.17). For Tihange, the tests of a positive gradient (Table 2) and the figure do not support the hypothesis of an increase in thyroid cancer incidence with increased wind direction frequency. For Mol-Dessel, the exposure–response curve supports the hypothesis of an increase in thyroid cancer incidence with wind direction frequency. However, the p values of the Stone's, LRS and LRS rank tests are not significant (p values = 0.36, 0.16 and 0.13, respectively). For Fleurus, the tests of a positive gradient were significant (p values <0.05 for all three tests) and the figure is suggestive for an increasing trend in thyroid cancer incidence with wind direction frequency.

Modeling of the hypothetical discharges of iodine-131 was performed for the two Belgian nuclear sites that showed higher SIR of thyroid cancer within the 20 km around the sites (data not shown), that is, the sites of Mol-Dessel and Fleurus. Figure 4 visualizes the RR of thyroid cancer incidence as a smooth function of the logarithm of the hypothetical radioactive discharge estimates. When dealing with skewed data, the log transformation decreases the variability of data and makes data conform more closely to the normal distribution. For Mol-Dessel, the exposure–response curve may suggest a very slight increase in thyroid cancer incidence. None of the tests of a gradient was however significant: the p values of the Stone's, LRS and LRS rank tests were 0.30, 0.23 and 0.27, respectively. For Fleurus, the exposure–response curve shows a global increasing trend in thyroid cancer incidence with increasing exposure. The tests of the gradient were significant (p values <0.001 for all three tests).

Discussion

The present study investigated whether there is an excess incidence of thyroid cancer in populations living close to the nuclear sites at the smallest Belgian geographical level. No evidence was found for more incident cases of thyroid cancer near the nuclear power plants of Doel and Tihange. Regarding the industrial and research nuclear sites, no evidence for a higher incidence in the vicinity of Mol-Dessel was observed. A slightly nonsignificant higher incidence was found in the close vicinity of Fleurus and significant gradients for thyroid cancer incidence were observed with the different types of exposure considered in the 20 km area around the site.

The study aimed to investigate the health effects of living near nuclear sites in Belgium, using an ecological design. Ecological studies have drawbacks because they are descriptive and do not allow inferring causal relationships on the origin of variations in incidence. Nevertheless, there is a real rationale for their conduct: cancer risks near nuclear facilities are of scientific interest because these facilities release radioactive substances. These substances emit ionizing radiation, which can cause cancer.[34] The aim of our study was not to investigate the Fleurus 2008 incident itself, the ecological design being not sensitive enough for the follow-up of single accidents. However, the time window of the available data covering the time of the incident, it was of interest to further investigate it. Standardized incidence rates before the incident were not significantly different from the rates after the incident. However, rates, especially among people having <30 years of age, are based on a small number of cases. The thyroid cancer incidence may not be sufficiently high to capture a potential start of increase. Radiation-induced thyroid cancers are characterized by a long latency period.[35–37] Even if thyroid cancer in young people is characterized by a shortened latency period,[35,38] the time window of the available data remains within the latency period and may therefore be too short to already pick up any possible increase in incidence. Moreover, short latencies concern high to very high exposures which are known to have the potential of causing thyroid cancer rather soon after exposure. Regarding a potential detection bias, we cannot exclude that people living near the nuclear sites are more likely to be detected with subclinical diseases, as a result of overdiagnosis. However, we did not find higher proportions of tumors of size T1 near Fleurus compared to the whole Walloon Region.

In the present investigation, we used cancer incidence data aggregated at the level of the statistical sector. Information on statistical sectors is available in the data coming from the Inter-Mutualistic Agency that is reliable from 2006. Consequently, the present study covered the years 2006–2014 but did not cover the years 2000–2005 for which cancer incidence data were available. The IMA-AIM databases contain information for each year, for all individuals registered in the mutual insurance companies. Almost all Belgians (98–99%) are registered, with valid and known residence and the differences with the total population appear mainly in the communes with cross-border workers or European officials. The exposure was estimated for the statistical sector of residence at the time of diagnosis. With local or small areas, it is more likely than for larger areas that the home address at the time of diagnosis and the daytime location, school or employment differ. However, compared to larger areas, such data minimizes the risk of misclassification of the residential exposure since the analysis is closer to the individual level.[19–21,25] In addition, compared to individual studies, the effect of exposure measurement error is reduced by averaging across groups.[19]

For rare diseases (small number of cases) and/or small areas (hence small population at risk), area-specific rate estimates such as standardized incidence ratios may be unstable because of chance variations related to small numbers. Rates estimated independently do not take into account nearby areas of the map, even though these are likely to be similar. To take account of spatial dependence of risks, we used a Bayesian hierarchical model. Such a model leads to improved and more stable estimates of the parameters of interest by increasing the amount of information used to estimate them.[25]

In ecological studies, data are compared at the population-level so that conclusions cannot be transferred to the individual level. The dose of radiation received by individuals depends not only on plant emission and geographic location but also on individual factors, behavioral factors and habits of life, such as possible genetic variations in thyroid cancer, radiation sensitivity, dietary intake of stable iodine, body mass, and medical examination.[9] In the present study, we did not account for the time spent in the exposed areas. Neither did we account for other environmental risk factors[39] nor individual characteristics, which could potentially confound the associations, as for example, the influence of iodine deficiency. Iodine deficiency is common in Chernobyl-contaminated regions and has been suggested to modify the effects of radiation since it increases the absorbed dose of radioiodine to the thyroid and stimulates cellular proliferation, leading to a possible tumor-promoting effect. The empirical data, however, are not entirely consistent on this point but iodine deficiency deserves careful attention in future studies of radiation-related thyroid cancer.[40] This point was also cited by the United Nations Scientific Committee on the Effects of Atomic Radiation (UNSCEAR) which recently published an evaluation of data on thyroid cancer in regions affected by the Chernobyl accident.[41] Regarding Belgium, the Belgian population was reported to be affected by iodine deficiency with a urinary iodine median concentration of 80 μg/l (in 1998).[42,43] In the last 10 years, Belgium has implemented measures on universal salt iodization (e.g., information campaigns, use of iodized salt in bakery products). The average dietary iodine intake of 15-to 64-year-olds has increased significantly from 53 μg

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per day in 2004 to 152 μg per day in 2014 (Belgian Food Consumption Survey[44]).

It was of interest to investigate whether the observed incidence pattern could be compatible with levels of radiation exposure from the sites. These levels of radioactivity of the surrounding air are often below the detection limit of the routine environmental monitoring in Belgium (TELERAD network). Therefore, we considered hypothetical radioactive discharges and used a model for computing hypothetical surrogate iodine-131 radioactive discharge estimates since measurements were not available. Limitations and uncertainties are inherent to the use of such a model in the situation at hand. The strictly hypothetical release from the sites was considered to take place under most probable meteorological and technical conditions to estimate an effective release height and the model error can be close to the spatial resolution of the data available at the statistical sector level. Moreover, the potential bias of measurement error may be more pronounced because it combines distance and wind direction misclassifications. However, this method is the radio-ecologically most plausible because it takes into account the behavior of radioactive substances atmospherically released to the environment to produce an exposure estimate for a population living nearby.

There are several types of thyroid cancer, classified according to their histopathological characteristics. Almost all (about 95%) thyroid cancers originate from cells of the follicular epithelium and are divided into papillary, follicular, and anaplastic forms. Papillary and follicular cancers are well-differentiated, while anaplastic cancers are poorly differentiated. Papillary carcinoma is the most frequent histological type (73%), followed by follicular carcinoma (15%), medullary carcinoma (5%), anaplastic carcinoma (3%) and other types (3%).[45] In a further step, when more incidence years become available, separate analyses for the different histologic forms of thyroid cancer as well as for different sizes of the tumor (based on the TNM classification) could be performed.

Around the two Belgian nuclear power plants of Doel and Tihange, we observed lower incidences of thyroid cancer compared to their reference area. A recent review and meta-analysis, which studied the risk of thyroid cancer associated with living near nuclear power plants, did not find increased risk of thyroid cancer overall (summary Odd Ratio = 0.98, 95% confidence interval: 0.87;1.11).[46] For studies considered as well-designed studies, the summary Odd Ratio was 1.13 (95% confidence interval: 0.69;1.84). Since this meta-analysis publication, Wang *et al.* studied cancer incidences in Taiwan for the period 1979–2003.[47] Thyroid cancer incidence was not different between the group of inhabitants living in the townships where nuclear power plants are located and the "nonplant-vicinity" group, these groups including 48 and 25 cases, respectively. In France, a significantly lower risk of thyroid cancer was observed in women living in the 20 km proximity area of the seven nuclear power plants under study (RR = 0.86, 95% CI: 0.77;0.96).[48] The authors suggest that a possible difference in medical practices might explain the results.

The present study is a follow-up of the Nucabel study which investigated the incidence of thyroid cancer around the Belgian nuclear sites at the level of the communes over the period 2000–2008 for the Flemish Region, 2004–2008 for the Walloon and Brussels Capital Regions[16,17] and more recently for the period 2000(2004)–2014.[15] For the nuclear site of Mol-Dessel, higher thyroid cancer incidence was suggested in the investigation at the level of the communes. No indication for a higher thyroid cancer incidence was observed in the investigation at the level of the statistical sectors. No significant gradient for thyroid cancer incidence with surrogate exposures (distance, wind direction frequency or hypothetical radioactive discharge estimates) was observed in the present analysis at the level of the statistical sectors for the period 2006–2014. Ecological bias and exposure misclassification were more likely to occur in the study at the level of the communes compared to the present study.

In conclusion, the present investigation at the smallest Belgian geographical level showed variations in thyroid cancer incidence around the Belgian nuclear sites. In addition, significant exposure–response relationships were observed for the site of Fleurus. Further investigations into these findings could be useful to allow inferring causal relationships on the origin of variations in incidence and to provide information at the individual level.

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