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Analyses of Temporal and Spatial Patterns of Glioblastoma Multiforme and other Brain Cancers Subtypes in Relation to Mobile Phones using Synthetic Counterfactuals.

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Abstract

This study assesses whether temporal trends in glioblastoma multiforme (GBM) in different brain regions, and of different malignant and benign (including acoustic neuroma and meningioma) subtypes in the temporal lobe, could be associated with mobile phone use.

Annual 1985-2005 incidence of brain cancer subtypes for England were linked to population-level covariates. Bayesian structural timeseries were used to create 2006-2014 counterfactual trends, and differences with measured newly diagnosed cases were interpreted as causal effects.

Increases in excess of the counterfactuals for GBM were found in the temporal (+38% [95% Credible Interval -7%,78%]) and frontal (+36% [-8%,77%]) lobes, which were in agreement with hypothesised temporal and spatial mechanisms of mobile phone usage, and cerebellum (+59% [-0%,120%]). However, effects were primarily present in older age groups, with largest effects in 75+ and 85+ groups, indicating mobile phone use is unlikely to have been an important putative factor. There was no evidence of an effect of mobile phone use on incidence of acoustic neuroma and meningioma.

Although 1985-2014 trends in GBM in the temporal and frontal lobes, and probably cerebellum, seem consistent with mobile phone use as an important putative factor, age-group specific analyses indicate that it is unlikely that this correlation is causal.

Highlights

- English 1985-2005 brain cancer subtype rates were compared to counterfactual trends
- Excess GBM increases were found in the frontal and temporal lobes, and cerebellum
- Mobile phone use was unlikely to have been an important putative factor
- No evidence of an effect of mobile phone use on acoustic neuroma and meningioma

Background

Although both the incidence of certain types of brain cancers (Khurana et al., 2009, de Vocht, 2016, de Vocht et al., 2011, Zada et al., 2012, Yang et al., 2017) and use of mobile phones (and other wireless technology) (Khurana et al., 2009) have been increasing over the last 2 decades, and despite extensive research it remains unclear whether this is a question of causation or correlation (Sienkiewicz et al., 2017). Based on all available evidence at the time, The International Agency for Research on Cancer (IARC) concluded in 2011 that exposure to radiofrequency radiation (RF) in the frequency range 30 kHz to 300 GHz, which includes the frequencies used by mobile phones (Cardis et al., 2011), should be classified as 2B (possibly carcinogenic to humans) taking into account positive associations between glioma and acoustic neuroma, and exposure to RF-EMF from wireless phones (Baan et al., 2011). Results from the National Toxicology Program (NTP) in rats seem to support this, with results suggesting an increased incidence of malignant glioma, as well as schwannomas of the heart in male, but not female, rats after whole-body averaged Specific Absorption Rate (SAR) levels that were comparable to the maximum localised SAR levels occurring in human head tissues located near to a mobile phone during a call (Wyde et al., 2016, NTP, 2018a, NTP, 2018b); however, there are some queries about these results, including their comparison with human exposures, and the study is yet to be published in peer-reviewed literature (Sienkiewicz et al., 2017).

It remains unclear what the biological mechanism for the association between GBM and exposure to radiofrequency radiation (RF) radiation from mobile phones would be, if an association were causal. Absorption of RF power leading to tissue heating has been argued to be the main mechanism by which RF can affect living tissue, but in the case of mobile phones it is unlikely to be sufficient to result in biological effects (Dewhirst et al., 2003). Alternative mechanisms have been proposed and include selective microthermal heating and dielectric

heating, as well as non-thermal iron ion-mediated reactions and radical pair mechanisms, as well as several other mechanisms considered less plausible (Sienkiewicz et al., 2017).

Monitoring of trends in brain tumour incidence rates was highlighted as an important research area, because it is unclear when any effect, if present, would be observable given the long lag between exposure and resulting clinical detection of brain cancers (Samet et al., 2014). Brain cancer incidence, including gliomas and especially an aggressive subtype, astrocytoma grade IV (glioblastoma multiforme [GBM]), have been increasing since the 1980s (Ostrom et al., 2014). A previous study based on English cancer incidence data and a novel causal inference framework based on synthetic counterfactuals indicated that the observed increase in malignant neoplasms in the temporal lobe between 1985-2014 was in agreement with mobile phone use as an important causal factor, but that for GBM, despite its incidence increasing over time as well, this did not deviate from expected, counterfactual, trends (de Vocht, 2016, de Vocht, 2017). Similar trends have been observed elsewhere (Ho et al., 2014, Kim et al., 2015, Ostrom et al., 2014, Zada et al., 2012), and improvements in diagnostics techniques, especially in the elderly, is generally considered the main explanation for the observed increase in incidence, while genetic risk factors and ionizing radiation exposure are known to increase the risk and allergic conditions appear to decrease it (Miranda-Filho et al., 2017) . A variety of other potential contributing factors have also been hypothesized to additionally explain these patterns, including hormonal contraceptives, hormone replacement therapy, statins, certain infections, a variety of occupational exposures, vitamin D, alcohol, height, BMI, as well as non-ionizing radiation including RF from mobile phones (Kim et al., 2015, Miranda-Filho et al., 2017, Philips et al., 2018).

This paper further expands on previous analyses and utilises the strengths of the Bayesian causal inference work using synthetic counterfactuals to explore the likelihood of mobile phone use as the important putative factor explaining the increases in the incidence of GBM in

different anatomic brain regions and for specific malignant (other than GBM) and benign (acoustic neuroma and meningioma) subtypes in the temporal lobe specifically (based on the results from the previous study (de Vocht, 2016)).

Methods

Data

National annual numbers of newly registered cases of malignant and benign neoplasms in the temporal lobe, based on 4-digit ICD-9 (up to 1995) and ICD-10 (post-1995) and 5-digit ICD-02 morphology codes, were obtained for the years 1985 to 2014 from the UK Office of National Statistics.

Covariates used to construct the counterfactual time series (see Statistical Methodology) included, similar to (de Vocht, 2016), annual incidence of all malignant neoplasms (except for non-melanoma skin cancer), population prevalence of current and never smokers, urbanization rate, and the percentage of status 3 records (record failed one or several vital validation checks on fields which are vital for inclusion in ONS tables) as a quality measure of coding, and were obtained from ONS (ONS, 2016), the Health Survey for England ((HSCIC), 2015) and the Worldbank (Worldbank, 2016). Annual population estimates and median age of the UK population were replaced by age category (0-24, 25-44, 45-64, 65+ years of age; as well as 75+ and 85+ years of age) specific population estimates to incorporate changes in demographics over the time period. Annual incidence of all brain cancers was included as a covariate and, to also account for changes in medical imaging practice in the UK, the annual total number of X-rays, CT, MRI, ultrasound, fluoroscopies and radio-isotope scans (as one total number) obtained from the NHS for the years 1995-2014 ((Operations), 2014) and extrapolated backwards, was also included.

Mobile phone use was estimated from the national number of cellular mobile phone subscriptions obtained and was obtained from the United Nations specialized agency for information and communication technologies (ITU) (ITU, 2016).

All non-cancer data are available as open access, while the cancer data were obtained after a Data Access Agreement with ONS was put in place prior to release of these data to the researcher.

Statistical Methodology

Bayesian structural time-series models in which the explanatory variables are functions of time and the parameters are time-varying were used. The methodology is described in detail elsewhere (Brodersen K. H. et al., 2015, Scott and Varian, 2014) and was used in previous analyses which informed the current analyses (de Vocht, 2016). In summary, structural time-series models are based on state-space models, which distinguish between a state equation that describes the transition of a set of latent variables from one time point to the next and an observation equation that specifies how a given system state relates to measurements (Brodersen K. H. et al., 2015). Kalman filtering is used for time series decomposition and the errors of different state-component models are assumed to be independent. Bayesian spike-and-slab priors are placed on the regression coefficients to enable selection of predictors, with the “spike” determining the probability of a non-zero coefficient based on independent Bernoulli distributions, and the “slab” a weakly informative Gaussian prior with a large variance (George and McCulloch, 1997). The model uses Bayesian model averaging to combine results and includes a regression component which enables the construction of a synthetic time series (*i.e.* the counterfactual). The posterior predictive density is then a joint distribution over all counterfactual data points (Brodersen K. H. et al., 2015), and through

subtraction of the counterfactual from the measured time series at each point in time, a semiparametric Bayesian posterior distribution for the causal effect is obtained.

Prior distributions for the variance are set as Gamma distributions and posterior simulation is done using a Gibbs sampler and Kalman filter (Durbin and Koopman, 2002) to simulate from a Markov chain with a stationary distribution. Priors for σ , initial value for σ and its upper value were set to 20%, 20% and 150% of the standard deviations in the outcome prior to forecasting of the counterfactual (1985-2005; see below), and the prior and initial values for μ were set to the standard deviation and first value of this period. Prior probability of inclusion of each covariate was set to 50% and the prior degrees of freedom to 20 (i.e. the number of years for modelling minus 1), and the prior expected explained variance and expected model size were set to 77% and 5 covariates, respectively, based on an initial trial run. All analyses were based on 100,000 Markov Chain Monte Carlo (MCMC) iterations to satisfy all diagnostic criteria (Heidelberger-Welch diagnostic stationary test, Heidelberg-Welch halfwidth, and Durbin-Watson tests), Raftery and Lewis' diagnostic (Dependence factor <5), Geweke test $< |1.96|$, and visual inspection of ACF/PACF autocorrelation plots). Bayesian tail-area probabilities were calculated and interpreted as classical p-values (Vehtari and Ojanen, 2012).

A 10-year lag between the introduction of mobile phones (for which, similar to previous analyses, the year 1995 was used, when the penetration rate in the UK passed 10% (ITU, 2016)) and it was assumed that any effect on the incidence rates would be measurable; in other words, time series from the year 1985 to 2005 were used to create the counterfactual and differences between the 2006-2014 measured numbers of annual newly diagnosed cases and the counterfactuals was interpreted as the causal effect. Following this, for those outcomes where a causal effect was observed, inclusion of the national mobile phone penetration rates should, if an important putative factor, explain, at least in part, observed excesses.

Sensitivity analyses were conducted assuming 0, 5 and 15-year lags to test this hypothesis (Online Supplementary Materials).

All analyses were conducted in *R* (version 3.2.4) using the *bsts* (Scott, 2017) and *CausalImpact* (H. and Hauser, 2017) packages.

Results

Results of the assessments of the time-series of annual newly diagnosed cases of GBM in anatomical regions of the brain compared to their forecasted counterfactuals are shown in Table 1. The number of newly diagnosed cases of GBM was higher than expected in the Frontal (+35.8% [95% Bayesian Credible Interval (BCI) -7.7%, 76.7%]; Bayesian tail-area probability (p-value) 0.05) and Temporal (+37.6% [95%BCI -6.6%, 77.6%]; p-value 0.05) lobes, as well as in the Cerebellum (+58.5% [-0.0%, +120.3%]; 0.03). Sensitivity analyses (Online Supplementary Material Table S1) indicate that these effects were not present for other modelled lag periods. These sensitivity analyses also indicated a deviance from the counterfactual for malignant neoplasm in the Cerebrum, but only when no lag was assumed (positive effect) and for 15-year modelled lag (negative effect).

Table 2 describes the results for the analyses of trend in newly diagnosed cases of subtypes of brain cancers and benign neoplasms in the temporal lobe. Newly diagnosed cases of primary malignant neoplasms in the temporal lobe have increased faster post-2005 than the counterfactual predicted; with an estimated additional increase of 33.1% (95% BCI 9.8%, 54.4%), which corresponds to 1,659 cases over the 2006-2014 period. The analysis of specific subtypes provides some evidence that gliomas ‘not otherwise specified’ (NOS) have increased beyond expectation, although the estimate of the causal effect is very imprecise (95% BCI -16.8%, 372.8%). There is stronger evidence that the increase of all malignant neoplasms in the

temporal lobe was more specifically an excess in newly diagnosed cases of GBM (+37.6% [95%BCI -6.6%, 77.6%]; p-value 0.05) and anaplastic astrocytoma (+45.2% [95%BCI 8.1%, 79.3%]; p-value 0.01). There was no evidence of other astrocytoma subtypes or of oligodendrogliomas deviating from expected, counterfactual, trends. These analyses further also do not support an association between the introduction of mobile phones and increased incidence of benign neoplasms (-5.2% [-29.1%, 16.9%]), nor for meningioma (-39.1% [-344.4%, 394.4%]) or acoustic neuroma (-7.7% [-38.7%, 20.4%]) specifically. Sensitivity analyses in which the hypothesized lag is changed to 0 years, 5 years or 15 years show that for these alternative lags nearly all observed temporal trends are comparable to the counterfactuals. The only exceptions are all malignant neoplasms in the temporal lobe, which also shows a +36% excess when no lag is assumed, but not for 5 and 15 years, and anaplastic oligodendroglioma, for which an excess effect is found for 0 years and a reduction in newly diagnosed cases for a 15-year lag. Neither of these point towards mobile phones being an important risk factor (Online Supplementary Materials Table S2).

To assess whether mobile phone usage could be an important putative factor, the national mobile phone penetration rate (assuming a 5-year lag) was included in the models for GBM in the anatomic regions and for subtypes in the temporal lobe with excess incidence post-2005 (Table 3). Inclusion reduced the effect size 61% and 75% for GBM in the frontal and temporal lobes, but not for those in the Cerebellum. Within the temporal lobe, mobile phone penetration rates also reduced the effect size for all malignant neoplasms and glioma (NOS) by about 50%, but had no effect on the observed impact on anaplastic astrocytoma.

Additional Age-group specific analyses were conducted to assess whether excesses in newly diagnosed cases in the temporal lobe compared to the counterfactuals were distributed evenly across age groups or were located in specific age groups, and explore how this impacts on the likelihood of mobile phone usage being an important putative factor. Results are provided in

Table 4 and also shown graphically in Figure 1. Excess, compared to the counterfactuals, including numbers of newly diagnosed cases of all malignant neoplasms in the temporal lobe and of GBM specifically were primarily observed for those over 45 years of age, which corresponds to the likely ages “first adopters” would have had. Inclusion of mobile phone penetration rates however, only affected the effect size for GBM and not for all malignant neoplasms. Moreover, the effect size of both all malignant neoplasms and GBM in the temporal lobe increases with older age groups from about 30% in those aged 45-64 when diagnosed, to about 45% for the 65+ age group, and to 50-80% and 127-177% for the 75+ and 85+ age groups, respectively. These trends correspond to a decreasing likelihood that these were “early adopters” (for example, the 85+ group would have been about 60+ years of age when relevant exposure occurred). On the other side of the age spectrum, excess incidence of all malignant neoplasms in the temporal lobe (but not for GBM) was also observed for the 0-24 years of age group (41.0% [-32.%, 84.4%]) which reduced to +4.5% (-2.1%, 102.4%) after inclusion of the mobile phone penetration rate into the models, which is also unlikely to have been the result of mobile phone use.

Discussion

This research aimed to further assess the likelihood of mobile phone use being an important putative cause for the observed increased incidence of glioblastoma multiforme and malignant and benign neoplasms in the temporal lobe from the 1980s.

A slightly higher impact of +37.6% was observed for all malignant neoplasms in the temporal lobe compared to the previous analysis (+35%) (de Vocht, 2016), because a later update of the national cancer registry database was used in this study and some additional covariates were included to calculate the counterfactuals.

Assessment of specific cancer subtypes in the temporal lobe indicated that the excess incidence was mainly found for GBM, with similar trends observed in the frontal lobe and cerebellum. Increased incidence rates of GBM have previously been reported elsewhere, but not everywhere, as well (Ostrom et al., 2014). The increased rates of specific brain cancer subtypes in excess of the counterfactuals correspond to the spatial and temporal patterns that would be expected if exposure to RF from mobile phones were an important putative factor (Cardis et al., 2008, Morgan et al., 2016), and mobile phone use has been associated with higher mutant type p53 gene expression in the peripheral zone of the glioblastoma (Akhavan-Sigari et al., 2014) and with decreased survival of GBM patients (Carlberg and Hardell, 2014, Akhavan-Sigari et al., 2014). However, age group-specific analyses indicate that the excess relative impacts increased with age over 65 years and were primarily found in the very old (75/85+ years of age) for whom it is unlikely that mobile phone use had been an important causal factor. In addition, excess numbers of newly diagnosed cases were also observed in the young (<24 years of age) for whom mobile phone use is also an unlikely causal factor.

Combining these results indicates that the likelihood of mobile phone usage being an important putative factor for the observed increases in primarily GBM since the 1980s is small, and that some other factor may be the cause and would have occurred in over a comparable time period. Analyses from other regions came to the same conclusion as this study (Kim et al., 2015, Sato et al., 2016, Zada et al., 2012), while previous analyses of English national GBM age-standardized rates for 5-year groups similarly showed an increase from 1995-99 to 2011-15 for most age groups, but with a steep increase in the rates for those 65 years of age and above, increasing with age (Philips et al., 2018). However, the authors of the latter study did not sufficiently discuss the implications of this age distribution for the interpretation of their results, while also because of the analytical method used they could not make comparisons with expected, counterfactual, trends in incidence rates.

In addition, these analyses provide no evidence for an association between mobile phone use and increased risk of benign neoplasms, including meningioma and acoustic neuroma specifically; temporal trends did not differ substantially from their counterfactuals. For meningioma these results were in agreement with data from Interphone and other case-control studies (Carlberg and Hardell, 2015, Group, 2010, Schuz et al., 2006), but for acoustic neuroma increased risks were observed for highest exposure levels (Hardell et al., 2013, Group, 2011). The latter may be because acoustic neuroma is a slow growing tumour, and the 10-year lag in our analyses may not have been sufficient; although there was also no evidence of an increase for the 15-year lagged sensitivity analysis.

If exposure to radiofrequency radiation from mobile phones is not the driving factor behind the observed excesses in primarily GBM rates, it is interesting to speculate what this other factor could be. Several candidates have been mentioned (Miranda-Filho et al., 2017), including some of environmental origin (Philips et al., 2018), but alternatively it has been suggested that the observed increase in the incidence of GBM is the result of improved diagnosis techniques, especially at older age (Kim et al., 2015, Zada et al., 2012, Davis et al., 1990, Greig et al., 1990), and improvements in classifications of gliomas, including the increased use of molecular markers (Ludwig and Kornblum, 2017) . The current analyses seem to support the latter interpretation, at least in so far as a main driving factor is considered, and this is further strengthened by the patterns observed for newly diagnosed cases of GBM in overlapping lesions or of an unspecified nature. This would however, not explain the observed excess in newly diagnosed cases of malignant neoplasms (but not GBM alone) in the temporal lobe in the under-24 age group. This could be a chance finding, but it has also been highlighted that secondary glioblastoma progress from low-grade diffuse or anaplastic astrocytoma, rather than *de novo* glioblastomas in elderly patients, make up the vast majority of glioblastomas in younger patients (Philips et al., 2018), or may occur as a result of different prenatal or early-

life exposure(s) of which RF from other sources or extremely-low electromagnetic fields also cannot be completely excluded (Mortazavi et al., 2017). It has been argued that the observed increase in GBM cannot solely be ascribed to improvements in diagnostic techniques because it affects specific areas in the brain only (Philips et al., 2018), which may indeed imply that exposure to RF from mobile phones cannot be excluded completely as a contributing factor, especially since the brain regions identified as showing an excess compared to their counterfactuals are those that absorb 81-86% of all mobile phone radiation (Cardis et al., 2008, Morgan et al., 2016). However, the region-specific analyses in this study were suggestive of comparable patterns compared to the counterfactuals in the occipital and cerebral lobes as well, suggesting effects may be less strong, but not exclusive to the aforementioned anatomic regions. Most likely the observed trends are the result of a combination of different factors, environmental and/or other (Miranda-Filho et al., 2017, Ostrom et al., 2014), and which may include mobile phone usage. Regardless, although this study (nor any of the previous ones) can unambiguously in- or exclude mobile phone usage as a contributing causal factor, data are broadly in agreement that the contribution of mobile phone usage in causing GBM or other types of brain cancer, if any, is likely to be small.

This study has several important limitations. Foremost, the inference made about the (causal) effects rely on the assumption that the relationships between the numbers of newly diagnosed cases and the variables in the model on which the counterfactuals are based remain consistent before and after the hypothesised point where an effect from the introduction of mobile phones would be measurable in national statistics.

The assumption that a 10-year lag was the most plausible period between first exposure and when increased risk could be observed in registry data was based on the previous analyses (de

Vocht, 2016). Although sensitivity analysis using a 15-year lag showed no evidence of excesses relative to counterfactuals, this may still have been too short. It has, however, been observed that the 10-year lag corresponds to a plausible maximum impact after first introduction of mobile phones in society of several decades (Ahlbom et al., 2009); a pattern that was previously also observed for asbestos and cancers in atomic bomb survivors (Walker, 1984, Furukawa et al., 2009). Although inconsistencies in coding and coverage could affect the evaluation of time series of cancer incidence (Zada et al., 2012) the UK cancer registry is considered to be of high quality (IARC, 2017); it seems therefore unlikely any coding errors would have significantly impacted on these results. However, improvement in diagnostic techniques and practices (other than the number of scans alone, which was included in these analyses), especially in the elderly, seems a plausible explanation for the observed effects, at least in part, and has happened roughly over the same time period as the introduction of mobile phones into society (Davis et al., 1990, Greig et al., 1990).

Despite its rigorous methodology and testing of *a priori* specified hypotheses, this remains an ecological study with its known limitations, including the ecological fallacy. Moreover, no quantitative data were available on other potential putative factors, environmental, diagnostic or otherwise, for inclusion in the models. This would be beneficial for future work. Information on laterality would also have been beneficial to further strengthen the inferences (Carlberg and Hardell, 2015), but are similarly not available for these data.

The main strength of this research is the use of Bayesian structural time-series and the use of synthetic counterfactuals, which are a flexible approach to modelling and forecasting of time series and, given certain assumptions, here enable the distinction between the temporal increases in newly diagnosed cases of brain cancer subtypes which are nonetheless not different

from expected trends and those that are in excess of expected, counterfactual, trends. In addition, this methodology uses Bayesian model averaging to make estimation of the counterfactuals relatively insensitive to the specific choice of explanatory factors and model specifications. These analytic features provide a stronger causal framework compared to recent analyses of similar data from England relying solely on descriptive analyses of trends (Philips et al., 2018). A further strength is that these analyses are based on high-quality data, which enabled the thorough investigation of temporal trends in the incidence of specific brain cancer subtypes and benign neoplasms in the temporal lobe specifically, as well as of GBM in different anatomical regions of the brain.

Conclusions

This study, in agreement with other data from the UK and elsewhere, shows that the incidence of glioblastoma multiforme (astrocytoma grade IV) has increased significantly since the 1980s, especially in the frontal and temporal lobes and cerebellum. However, it further provides evidence that the trend of increasing numbers of newly diagnosed cases of glioblastoma multiforme in the temporal lobe (but likely in the frontal lobe and cerebellum as well) since the mid-1980s, although seemingly consistent with the hypothesis of exposure to radiofrequency radiation from mobile phones being an important putative factor, should to a large extent (if not exclusively) be attributed to another factor or factors; of which improvements in diagnostic techniques, especially in the elderly, seems the most plausible. Although these analyses indicate that it is unlikely that exposure to RF from mobile phones is an important putative factor, they also cannot exclude it as a contributing factor completely. It is therefore important to keep monitoring incidence trend data.

Table 1. Modelled causal effects for annual number of newly diagnosed cases of Glioblastoma multiforme (GBM) for different anatomic brain regions (1985-2014) assuming 10-year lag between exposure and measurable effect.

Table 2. Modelled causal effects for specific neoplasm subtypes in the temporal lobe with over 100 cases (1985-2014), assuming a 10-year lag between exposure and measurable effect.

Table 3. Comparison of modelled causal effects with and without the mobile phone penetration rate included in the Bayesian structural timeseries for selected cancer subtypes.

Table 4. Analyses of all malignant neoplasms and Glioblastoma multiforme (GBM) in the temporal lobe by age group.

Figure 1. Actual (solid line) and modelled counterfactual (dotted line) plus 95% Bayesian Credible Intervals (shaded area) 1985-2014 annual newly diagnosed cases of glioblastoma multiforme in the temporal lobe for different age groups.

Note that 75+ and 85+ age groups also included in 65+ group.

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