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Probabilistic Multiple-Bias Modeling Applied to the Canadian Data From the Interphone Study of Mobile Phone Use and Risk of Glioma, Meningioma, Acoustic Neuroma, and Parotid Gland Tumors

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We undertook a re-analysis of the Canadian data from the 13-country case-control Interphone Study (2001–2004), in which researchers evaluated the associations of mobile phone use with the risks of brain, acoustic neuroma, and parotid gland tumors. In the main publication of the multinational Interphone Study, investigators concluded that biases and errors prevented a causal interpretation. We applied a probabilistic multiple-bias model to address possible biases simultaneously, using validation data from billing records and nonparticipant questionnaires as information on recall error and selective participation. In our modeling, we sought to adjust for these sources of uncertainty and to facilitate interpretation. For glioma, when comparing those in the highest quartile of use (>558 lifetime hours) to those who were not regular users, the odds ratio was 2.0 (95% confidence interval: 1.2, 3.4). After adjustment for selection and recall biases, the odds ratio was 2.2 (95% limits: 1.3, 4.1). There was little evidence of an increase in the risk of meningioma, acoustic neuroma, or parotid gland tumors in relation to mobile phone use. Adjustments for selection and recall biases did not materially affect interpretation in our results from Canadian data.

bias; bias modeling; brain tumors; cancer; case-control study; head and neck tumors; mobile phones

Abbreviation: CI, confidence interval.

In Canada, the number of mobile phone subscribers rose from 6,000 in 1985 to approximately 29.4 million in 2015 (1). Health Canada implemented Safety Code 6 (2015) to limit exposures to radiofrequency electromagnetic fields based on thermal and possible nonthermal health effects (2), but increased use of mobile phones has nevertheless been accompanied by both public and scientific concern, in particular regarding brain tumors. Although a compelling mechanistic hypothesis has yet to be advanced whereby mobile phone non-ionizing radiofrequency exposure would be tumorigenic, in 2011, the International Agency for Research on Cancer classified radiofrequency exposures as possibly carcinogenic to humans (category 2B), largely based on results from epidemiologic studies (3).

Studies have focused on tumors originating closest to locations of exposure to the electromagnetic fields emitted from mobile phones while in use. Varied results have arisen from the Interphone Study (4, 5), the CEFALO Study (6), a Danish cohort study (7), and a pooled analysis of studies by Hardell and Carlberg (8). In a number of reviews, investigators have synthesized the evidence for an association between mobile phone use and the risk of brain tumors. Repacholi et al. (9) concluded that available evidence was consistent with no statistically significant relationship and that none of Hill's considerations (10) for causality were met. In contrast, Hardell and Carlberg (11) concluded from available evidence that radiofrequency exposure is causally associated with the risks of glioma and acoustic neuroma and that current exposure guidelines need revision.

It has been asserted that currently available evidence is flawed because of potential biases from selection factors and exposure misclassification (12, 13). The Interphone Study Group commented that "biases and errors prevent a causal interpretation" (4, p.1). Given the enormous public health interest and the likelihood that the tumorigenic effects of radiofrequency exposures,

if present, would be small and vulnerable to bias and random error, we undertook a probabilistic bias analysis (14) using the part of the Interphone Study for which data were available to us, namely the Canadian component.

Among possible sources of bias in the Interphone Study were errors in reported recall of mobile phone use and selection bias due to low and unrepresentative participation. A number of validation studies were conducted to assess bias in the study (15–20). Previous work focused on sensitivity of estimates to various scenarios of recall and selection biases, but our application of bias modeling is an attempt to provide a more reasonable set of estimates for the association of mobile phone use and the risks of head and neck tumors. Our bias models produced point and interval estimates that incorporated available information about several possible sources of systematic error (21).

METHODS

A case-control study was carried out in Canada as part of the Interphone Study (22). The source population was limited to Canadian citizens 30–59 years of age who resided in one of the 3 study regions (Greater Metropolitan Montréal; Ottawa and the Ottawa Valley; and metropolitan Vancouver, southwest British Columbia, and the Greater Victoria area). Ascertainment began in 2001 for acoustic neuroma and parotid gland tumors and 2002 for glioma and meningioma, and it ended in 2004.

Case series

All diagnoses were either histologically confirmed or based on unequivocal diagnostic imaging. Diagnoses included in the case series were primary incident cases of glioma, meningioma, acoustic neuroma, or malignant and benign parotid gland tumors.

In Montréal, cases were identified in the following hospitals: McGill University Hospital Center, Center Hospitalier de l'Université de Montréal, Jewish General Hospital, Hôpital du Sacré-Coeur de Montréal, Hôpital Charles Lemoyne, Cité de la Santé de Laval, St-Mary's Hospital, Hôpital Maisonneuve-Rosemont, and Montréal Neurological Institute. In Ottawa, cases were identified at The Ottawa Hospital. Acoustic neuroma and parotid gland tumor cases were recruited through all ear, nose, and throat specialists in the Ottawa catchment area, and only the Ottawa center ascertained benign parotid gland tumors. In Vancouver, diagnoses were identified from reports from all hospitals located in the study region, as well as from referral reports made available from the provincial BC Cancer Registry.

Combining the 4 tumor types, there were a total of 405 participating cases (Table 1). This represented response proportions of 63% for glioma, 71% for meningioma, 82% for acoustic neuroma, and 69% for parotid gland tumors.

Control series

Control subjects were matched on age (within 5 years), sex, and study region. In Montréal, electoral lists were used with frequency matching to identify controls, but for our matched analysis, we used the post hoc matched case-control sets implemented for Montréal by the International Agency for Research on Cancer in their original publication of pooled country results (4). In Ottawa, controls were individually matched and recruited using random digit dialing via an external company, Opinion Search (Ottawa, Canada). In Vancouver, individual matching was done by sampling from the population-based BC Ministry of Health Client Registry. One control was selected for each glioma and meningioma case, 2 were selected for acoustic neuroma cases, and 3 were selected for parotid gland cases.

Recruitment materials for both the case and control series made no mention of mobile phones in an attempt to avoid selective participation based on exposure. All relevant institutional ethics boards approved this study, and informed consent was obtained prior to study participation.

For the control series, 653 individuals were interviewed (response rate of 56%). Reasons for nonparticipation among both cases and controls included refusal, physician refusal, death, sickness, and language barriers.

Data collection and imputation

In-person interviews were conducted to elicit lifetime history of mobile phone usage. Photos of all mobile phone models that had been marketed in Canada were presented to respondents to help identify models, and questions were asked about patterns of use, network operators, use of hands-free devices, and use in urban and rural areas (see Cardis et al. (22) for further detail). Approximately 75% of Canadian participants agreed to allow us to retrieve their billing records from mobile phone operators, who provided records of outgoing and incoming calls. Individuals who refused participation in the full study were offered a short "nonrespondent" questionnaire that asked about mobile phone use. Of those who refused to participate, 162 of 516 controls (a 31% completion rate) completed the short nonrespondent questionnaire, whereas only 3 of 184 cases did. The proportion of individuals who reported regular mobile phone use was lower in the nonrespondent control group (41%) than in the respondent control group (53%).

Documentation of recalled mobile phone use allowed a variety of formats for the response, including missing values and range responses (e.g., "5 to 10 minutes per day of talk-time" or "first use began in the summer of 2001"). These responses were addressed with the same simple imputation algorithm that was used for the pooled Interphone analyses (Table 2 and Cardis et al. (22)), which depended on phone models, adjacent periods of a participant's usage, and region-specific phone use.

Statistical analyses

Analyses were performed separately for each of the 4 tumor types. To improve precision in this small Canadian data set, a decision was made to break the individual matching originally used in the International Agency for Research on Cancer analyses and to use a common pool of controls for each tumor-type analysis, with the study population stratified into 36 strata of sex, region, and 5-year age categories. The reference dates for cases were the dates of diagnosis. For each control, the reference date was assigned according to the original matched case. We used conditional logistic regression with the 36 strata and included adjustment for an ordinal variable that represented educational level and one for the product term of region by

Table 1. Characteristics of the Study Population, Interphone Study, Montréal, Ottawa, and Vancouver, Canada, 2001–2004

Characteristic	Glioma (n = 170)		Meningioma (n = 94)		Parotid Gland[a] (n = 57)		Acoustic Neuroma (n = 84)		Controls (n = 653)	
	No.	%	No.	%	No.	%	No.	%	No.	%
Region										
Montréal	65	38	48	51	9	16	33	39	234	36
Ottawa	25	15	15	16	35[a]	61	17	20	180	28
Vancouver	80	47	31	33	13	23	34	40	239	37
Educational level										
High school or less	67	39	42	45	18	32	27	32	188	29
Technical/professional	47	28	26	28	20	35	24	29	190	29
University graduate	43	25	16	17	14	25	18	21	166	25
Postgraduate university	13	8	10	11	5	9	15	18	109	17
Age, years										
30–34	18	11	2	2	6	11	3	4	59	9
35–39	23	14	7	7	12	21	8	10	80	12
40–44	20	12	10	11	10	18	16	19	106	16
45–49	34	20	20	21	9	16	19	23	117	18
50–54	31	18	27	29	10	18	20	24	128	20
55–59	44	26	28	30	10	18	18	21	163	25
Sex										
Male	109	64	27	29	26	46	37	44	322	49
Female	61	36	67	71	31	54	47	56	331	51

[a] The 35 cases of parotid tumors in Ottawa included 29 benign tumors, which were only ascertained for the study in the Ottawa region.

months since interviewing began. Although we considered a number of other confounders for the analyses, including history of allergic disorders, family cancer history, and smoking history (for gliomas), we nevertheless did not include them in the final models based on the conclusion from the international pooled data that these covariates did not confound the results (4). Use of a covariate for census tract income, a possible socioeconomic confounder, did not influence our results (data not shown).

Two exposure metrics were considered. The first (regular mobile phone use) was defined as a dichotomous variable based on an average of at least 1 call per week for a period of 6 months or more at some point in the past. The second exposure

Table 2. Methods of Data Cleaning and Imputation and Number of Subjects Affected, Interphone Study, Montréal, Ottawa, and Vancouver, Canada, 2001–2004

Problem	No. of Subjects Affected (n = 1,058)	Action
Missing dates or a range was reported for phone dates (year and month)	14 for year and 168 for month	Hierarchical order of imputation: 1. Calculated median from range given by subject. 2. Used midpoint of season or year if provided. 3. Used end of previous period.
Missing values or range was reported for no. or duration of calls	453	Hierarchical order of imputation: 1. Calculated median from range given by subject. 2. Used values from an adjacent period with complete data. 3. Imputed from median usage of similar users (within categories of sex and year of use).
Hands-free usage	62	Proportionally reduced usage by amount of time spent using hands-free device and proportion of calls made in vehicles (using hands-free device).
Missing value for educational level	3	Set to high-school value.

metric, which was categorized into quartiles, was derived to reflect lifetime cumulative hours of use (see the Appendix for an example). The reference category for both variables combined never use of a mobile phone, irregular use amounting to less than 1 call per week, or use only with a hands-free device. Exposure in the year preceding the reference date was also coded as nonexposure. Phone use was reduced by 25%, 50%, 75%, or 100% depending on use of hands-free devices less than half the time, half the time, more than half the time, or all the time, respectively.

We used sensitivity analyses to address results with respect to modeling choices and control matching options. To address a possible bias with respect to the timing of interviews, because controls tended to be interviewed after cases, another version of the post hoc matched sets were created under the condition that case and control interviews occurred within 1 year of each other.

Bias modeling

We used a simple approach to probabilistic multiple-bias modeling (23) that was designed expressly to provide bias-adjusted estimates over a range of plausible values for the bias parameters. To provide the best evidence of the magnitude and uncertainty of each bias factor, probability distributions were derived from the Interphone validation data for recall errors (Table 3) and subject-selection factors (Table 4). A Monte Carlo procedure was used to correct for biases in the opposite sequence in which they likely occurred in the study population (14). With the Interphone case-control design, one would expect that confounding occurred in the source population, followed by issues of selection of participants into the study population (by outcome and exposure status), and finally exposure measurement recall issues during interviews. Depending on the correctness of the bias model, this bias-adjustment method would reconstruct the study population that would purportedly have been observed if recall and selection biases had been absent.

In the first adjustment, which was for bias due to recall error, a continuous error model was used. Operator records were used to derive factors that would be applied as an adjustment to each individual's recalled phone use during each distinct pattern of use. Bland-Altman plots were provided in an Interphone validation substudy by Vrijheid et al. (17) in which they presented a comparison between recall of phone use by a subsample of Interphone respondents with actual operator records of usage among those individuals. Participating countries included Canada, Italy, and Australia, with records typically reflecting the most recent 2–5 years of phone use. This comparison demonstrated that light users tended to underestimate their use (number of calls, call duration), whereas heavy users tended to overestimate use, with an overall overestimation of duration of calls but an underestimation of number of calls. Fitted regression equations were taken directly from Bland-Altman plots, separately for cases and controls, with variables for recalled calls and operator reported calls, as well as estimated coefficient (β) and intercept (α). These regression equations were reconfigured to derive an adjustment factor dependent on the recalled number of calls, such that the adjustment factor for the number of calls per month would equal $[(\log(\text{recalled calls}) - \alpha - \beta \times \log(\text{recalled calls})/2)/(1 + \beta/2)]/\log(\text{recalled calls})$, with the coefficients α and β as estimated in Vrijheid et al. (17). Adjustment factors for recalled durations in minutes were derived similarly and in both cases were represented with a normal probability distribution. Variances were derived from the reported confidence intervals of the under- or overestimation of calls/durations in Vrijheid et al. (17), and the variance was assumed to be homoscedastic across the range of adjustment factors.

In the second adjustment, which was for selection probabilities, a discrete error model was used. The distribution of cell phone use could be derived for those nonparticipant cases and controls who filled in the nonrespondent questionnaire; these results could then be projected separately onto nonparticipant cases and controls who did not fill in the nonrespondent questionnaire to classify them as regular users or nonusers (24). Results from the entire Interphone data set (Cardis et al. (22)) were used to derive these selection probabilities because too few nonrespondent questionnaires were completed by cases in the Canadian study to reliably calculate these probabilities. To represent uncertainty in the actual value of the selection probabilities, trapezoidal probability distributions (a minimum, lower and upper modes, and maximum) were symmetrically centered

Table 3. Bias Parameters for Adjustment of Bias Due to Recall Error, With Assigned Values Used in the Probabilistic Multiple-Bias Modeling, Interphone Study, Montréal, Ottawa, and Vancouver, Canada, 2001–2004

Participant Category and Parameter	Normal Distribution[a]		
	α	β	Variance
Cases			
No. of calls	−1.89	0.42	0.005
Duration of calls	−2.55	0.55	0.008
Controls			
No. of calls	−1.77	0.35	0.005
Duration of calls	−1.94	0.41	0.008

[a] Adjustment of number of calls and duration of calls at predicted values of regression equations.

Table 4. Bias Parameters for Adjustment of Selection Bias, With Assigned Values Used in the Probabilistic Multiple-Bias Modeling, Interphone Study, Montréal, Ottawa, and Vancouver, Canada, 2001–2004

Participant Category	Trapezoidal Distribution			
	Minimum	Lower Mode	Upper Mode	Maximum
Cases				
Regular users	0.50	0.60	0.70	0.80
Not regular users	0.48	0.58	0.68	0.78
Controls				
Regular users	0.40	0.50	0.60	0.70
Not regular users	0.33	0.43	0.53	0.63

on the 4 derived selection probabilities for the different strata defined by case status and regular user status.

Each iteration of the procedure followed a predetermined sequence, with new adjustment factors drawn randomly in each iteration, saving the resulting logistic regression point estimate. First, for each distinct pattern of mobile phone use in each individual, 2 adjustment factors were drawn (see Table 3), 1 for number of calls and 1 for duration of calls, and multiplied by the natural logs of recalled number of calls and duration of calls, respectively. For example, if a case had recalled making 20 calls per month, a random adjustment factor for natural log(20) would be drawn from a normal distribution with mean of 1.17 (derived from the formula above) and variance of 0.005; had the adjustment factor been 1.17, the adjusted calls per month would be approximately 33. This was followed by drawing 4 selection probabilities for the case-control and user-nonuser tabulation (see Table 4). These probabilities were used to create a "missing persons" data set using a naive random sampling of the "recall-adjusted" study population with replication. For example, for the 86 case patients who were regular users and agreed to be in the study, had the drawn selection probability been 0.65, there would be an estimated 46 missed cases who were regular users (i.e., 86/0.65−86); the 46 individuals would be randomly sampled from the 86 study participants (after having their recall already adjusted), reconstituting 132 individuals. Finally, record-level adjustment for the measured covariates, such as educational level, was accomplished with traditional conditional logistic regression, and random error was reintroduced to the estimate using a variant of the Box-Mueller approach and based on the standard error estimated from the original data. For each tumor analyzed, stable confidence limits were achieved with 8,000 iterations. The median of the range of estimates was used as the new point estimate of the bias-adjusted association, and the 2.5th and 97.5th estimates were used as the new 95% limits. All analyses were performed using SAS, version 9.3 (SAS Institute, Inc., Cary, North Carolina).

RESULTS

Table 5 presents estimates from conditional logistic regression for dichotomous regular phone use. For glioma and parotid tumors, the odds ratio estimates were close to unity; for acoustic neuromas, the odds ratio was 0.7 (95% confidence interval (CI): 0.4, 1.2); and for meningiomas, the odds ratio was 1.3 (95% CI: 0.8, 2.0). When comparing the highest quartile (>558 hours) of cumulative hours of use (second and third quartiles collapsed) with the reference category, the odds ratio for glioma was 2.0 (95% CI: 1.2, 3.4).

Table 5 also provides results for the probabilistic bias modeling, reflecting the adjustment for only selection bias, only recall bias, and both biases simultaneously. The first 2 columns of bias adjustment results intentionally reflect only the probability distributions of the bias parameters and not random error, and thus the intervals are overly narrow. As expected, selection bias consistently resulted in a slightly greater odds ratio, with some of the estimates being raised from below unity to 1.0. Adjustment for the combined influence of recall errors on number and duration of calls resulted in typically negligible increases in odds ratio with some exceptions, such as for some meningioma results. The final column of Table 5 re-introduces random error (as is normally found in the conventional confidence interval) to the model that combines the 2 types of systematic error.

We used sensitivity analyses to address various uses of controls and modeling choices. From our main analysis, the glioma-specific estimate from the conditional logistic model with 653 pooled controls and 36 collapsed strata resulted in an odds ratio of 2.0 (95% CI: 1.2, 3.4) for the highest quartile of cumulative phone use. Reducing the pool of controls to only the original 170 matched glioma controls and again collapsing the pairs into 36 strata produced an odds ratio of 1.9 (95% CI: 1.0, 3.7). A traditional approach with 170 strata of original 1:1 matched pairs produced an odds ratio of 1.4 (95% CI: 0.7, 2.8). Alternatively, to address a potential issue due to delays in interviewing controls, 1:M post hoc matching (producing 1 case matched to a variable number M of controls) that prioritized closest case: control dates of interview resulted in an odds ratio of 1.8 (95% CI: 1.0, 3.2). The narrowest 95% limits were provided by our a priori choice.

DISCUSSION

In the present article, we present a re-analysis of the Canadian data from the Interphone Study. These data were originally only reported pooled with other countries in international publications (4, 5, 25). In contrast to the previous Interphone publications in which bias in sensitivity analyses was addressed with individual simple adjustments, we have attempted an approach to bias-adjustment in order to provide a single set of potentially more causally interpretable results after correcting for 2 possible biases simultaneously. Using a logistic regression modeling strategy different from that used in previous studies of Interphone data and based on a subset of the Interphone data set, we found results that were broadly consistent with the range of results observed in the entire international study for meningiomas (4) and acoustic neuromas (5). Although an international analysis of parotid gland tumors has not been published, the results for Canada are consistent with those reported in a combined analysis of the data from Denmark and Sweden (26). The odds ratio of 2.0 for gliomas in the highest cumulative exposure category (>558 hours of cumulative call time) in the Canadian study is higher than the value of 1.4 in the highest cumulative exposure category (≥1,640 hours) in the international study (4). This may simply reflect sampling variability, differential biases between study centers, differences in matching strategies, or real differences in risk related to different communication technologies between Canada and other Interphone countries (see Appendix of Cardis et al. (27)).

The focus of the present analyses was the introduction of bias adjustment methods, the use of which provided point and interval estimates in the context of a structure that addressed the 2 most likely sources of bias. Although all epidemiologic results need to be interpreted through the lens of an often unspecified bias structure, the validity of bias-adjusted results is conditional on an explicit model for bias. To the extent that our bias model is accurately specified, the simultaneous adjustment for both selection and recall bias resulted in only a small

Table 5. Conditional Logistic and Bias-Adjusted Odds Ratios for Phone Use by Tumor Type, Interphone Study, Montréal, Ottawa, and Vancouver, Canada, 2001–2004

Tumor Type and Exposure Metric	No. of Cases	No. of Controls	OR[a]	95% CI	Bias Modeling Adjustment					
					Bias Due to Recall Error[b]		Selection Bias[b]		Recall and Selection Biases, With Random Error	
					OR	95% Limits	OR	95% Limits	OR	95% Limits
Glioma										
Reference level[c]	89	339	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
Regular use	81	314	1.0	0.7, 1.5	NA[d]	NA	1.1	1.0, 1.2	1.1	0.7, 1.6
Cumulative no. of hours										
<40	14	77	0.9	0.4, 1.7	0.8	0.7, 0.9	1.0	0.7, 1.3	0.9	0.4, 1.8
40–558	35	163	0.7	0.4, 1.2	0.7	0.6, 0.8	0.8	0.6, 1.0	0.8	0.4, 1.4
>558	32	74	2.0	1.2, 3.4	2.0	1.8, 2.1	2.3	1.9, 2.8	2.2	1.3, 4.1
Meningioma										
Reference level[c]	52	339	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
Regular use	42	314	1.3	0.8, 2.0	NA	NA	1.4	1.2, 1.6	1.4	0.8, 2.2
Cumulative no. of hours										
<40	13	77	1.3	0.7, 2.7	1.5	1.2, 1.7	1.5	1.1, 2.0	1.6	0.8, 3.6
40–558	22	163	1.3	0.7, 2.4	1.1	0.9, 1.2	1.5	1.2, 1.8	1.2	0.6, 2.3
>558	7	74	1.0	0.4, 2.4	1.3	1.1, 1.5	1.1	0.7, 1.5	1.4	0.5, 3.6
Parotid gland										
Reference level[c]	29	339	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
Regular use	28	314	0.9	0.5, 1.6	NA	NA	1.0	0.9, 1.1	1.0	0.5, 1.7
Cumulative no. of hours										
<40	9	77	1.0	0.4, 2.3	0.9	0.7, 0.9	1.1	0.8, 1.5	0.9	0.4, 2.3
40–558	15	163	1.0	0.5, 2.1	1.0	1.0, 1.1	1.2	0.9, 1.5	1.2	0.5, 2.5
>558	4	74	0.5	0.2, 1.6	0.5	0.5, 0.6	0.5	0.3, 0.9	0.5	0.1, 1.8
Acoustic neuroma										
Reference level[c]	50	339	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
Regular use	34	314	0.7	0.4, 1.2	NA	NA	0.8	0.7, 0.9	0.7	0.4, 1.2
Cumulative no. of hours										
<40	12	77	1.1	0.5, 2.2	0.9	0.8, 1.0	1.2	0.9, 1.6	1.0	0.5, 2.2
40–558	14	163	0.5	0.3, 1.1	0.6	0.5, 0.6	0.6	0.4, 0.8	0.6	0.3, 1.3
>558	8	74	0.7	0.3, 1.6	0.7	0.6, 0.7	0.7	0.5, 1.0	0.7	0.3, 1.8

Abbreviations: CI, confidence interval; NA, not applicable; OR, odds ratio.

[a] Conditional logistic regression modeling stratified on age, sex, and region, with further regression adjustment for educational level and interview lag.

[b] The 95% interval estimates for 2 columns (recall bias and selection bias) only reflect probability distributions of bias parameters; without random error, these intervals are overly narrow.

[c] Reference level defined as never use, irregular use, use within a year before reference date, or use only with hands-free devices.

[d] NA for bias modeling under adjustment for bias due to recall error reflects that users were never reclassified to nonuser status in the model.

change from conventional modeling results and would not suggest a different interpretation. This small change differs from the sensitivity analyses in the pooled Interphone publication, in which restricting to ever regular users as a means of addressing possible selection bias notably increased the estimated odds ratio for glioma from 1.4 to 1.8 in the highest decile of use (Appendix 2 of reference 4). Aside from the odds ratio for glioma risk, no other results were consistent with an

interpretation of increased risk, even considering adjustment for likely biases. We do not claim that the Canadian estimates are more valid than those of the entire Interphone population; however, the present analysis provides some perspective on interpretation as well as on the degree of bias that might be present in the entire Interphone data set if 2 sources of bias were taken into account.

In inferring the public health implications of the results of the Interphone Study and our bias modeling, it is important to recognize the manner in which use of wireless telecommunications devices continues to evolve. Despite an increasing preference for texting and use of social media, particularly among the young, the use of mobile phones for calling is still substantial, with little evidence of decreases over the last decade (E. Cardis, ISGlobal, personal communication, 2016), which suggests that epidemiologic studies of this issue are still relevant.

Bias models can shift the discussion toward an explicit and quantitative appreciation of the correctness of the assumed bias structure (28), avoiding what some have described as more qualitative discussions of bias (23). Although our regular conditional logistic model implicitly assumed no recall bias and no selective recruitment, our bias model was based on validation data that was used to inform the presence and magnitude of these errors. There are nevertheless a number of limitations with our approach to bias modeling. Although we adjusted for some measured covariates in our regression models and the Interphone publication suggested little confounding from other measured candidate confounders, residual confounding due to unmeasured covariates, which we did not address in our bias modeling, might still be possible. We undertook only simple imputation for recalled calendar dates and assumed that this recall was without error. We made 2 simplifying assumptions: that the recall errors within individuals for different periods of use were independent and, in the adjustment for selection bias, that the extent of use (duration and number of calls) in nonrespondents was the same as in respondents (although the tabulated frequencies of users and nonusers were not). This was implicit in our sampling with replacement procedure. Finally, our model did not factor in the fact that in 1 validation study (17), there was some evidence that overestimation of phone use was more likely in more distant time periods. In our implementation, we applied adjustment factors derived from data on relatively recent use (2–5 years) to recall across each individual's lifetime. Our validation results are derived from combined histological case types, such that arguably different tumor types might require different bias adjustments. As participation in research studies may involve complex relationships with social and cultural factors (29), it may be questionable to rely on international data to derive selection bias adjustments in the Canadian data. Furthermore, because not all nonparticipants agreed to complete the nonrespondent questionnaire, there remains a possibility that the information collected does not accurately reflect all nonparticipants. Despite these limitations, fairly wide probability distributions were placed on all bias parameters, effectively including a wide range of possible bias adjustment scenarios, which will be reflected in the resulting 95% Monte Carlo interval estimates.

As an algebraic check on the Monte Carlo simulations performed here, the logistic regression odds ratio of 1.0—for regular use of a mobile phone on risk of glioma—can be bias-adjusted by multiplying by the inverse of the expected selection odds ratio $(0.65\times0.48)/(0.55\times0.63)$, resulting in an odds ratio of 1.1. Given the validation results showing errors in opposite direction for recalled duration and number of calls, the averaged influence of recall error would possibly be minimal.

We also performed classical sensitivity analyses that highlight that various defensible choices concerning matching and analysis strategy, although sometimes arbitrary, can influence results. Our selection of sensitivity analyses does not obviate the fact that all epidemiologic analyses involve a number of somewhat subjective analytic choices. Although our primary model resulted in the largest odds ratio, it was chosen a priori as a valid approach that would also improve precision. Despite smaller odds ratios with the other matching and modeling strategies, the results were always consistent with an increased magnitude of association with glioma, regardless of method. Of note, most of these matching strategies may have permitted subtle bias in the interplay of calendar trends and recall, whereby recall of earlier phone use patterns was influenced by more recent use. The issue may have manifested with most controls tending to be interviewed long after cases in calendar time and having their exposure truncated to the case reference dates. An alternative approach, where post hoc matching prioritized similar interviewing dates between cases and controls, resulted in an odds ratio (1.8) similar to that using our chosen strategy (2.0).

Unlike in the Canadian data, the Interphone multinational data showed a markedly decreased risk associated with most measures of phone use and an increased risk only in the highest decile of use. The study group concluded that "biases and errors prevent a causal interpretation" (4, p.1). To the extent that the bias model applied in the present re-analysis of the Canadian data is reasonable, conventional modeling of existing data likely resulted in slight underestimation of the magnitude of associations; however, interpretation of bias-adjusted results would not have materially changed from the original Canadian results.

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APPENDIX

Example of Cumulative Exposure Coding

By way of example, assume a study subject with a newly diagnosed brain tumor reported using a mobile phone in 2 distinct patterns preceding the diagnosis, with the first pattern beginning 5 years in the past and including 2–4 calls per day, each approximately 1 minute long. With the second pattern, which began 2 years before the diagnosis, this person's pattern of use changed; the subject now recalls approximately 20 calls per month and approximately 100 minutes per month of use, but half the calls were made while driving, always with a hands-free kit. This person would be categorized as a regular user based the first pattern of use because he or she made calls in excess of once per week for at least 6 months. The number of calls in the first pattern would be averaged to 3 calls per day, amounting to approximately 3 minutes of use per day for 3 years. The second pattern would be truncated to 1 year of accumulated exposure (discarding the year preceding the diagnosis), and given hands-free use, exposure would also be reduced to 50 minutes per month, or 1.6 minutes per day for 1 year. Cumulative hours of use would be reported as approximately 64.5 hours.