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The effects of recall errors and of selection bias in epidemiologic studies of mobile phone use and cancer risk

MARTINE VRIJHEID[a], ISABELLE DELTOUR[a], DANIEL KREWSKI[a,b], MARIE SANCHEZ[a] AND ELISABETH CARDIS[a]

[a]*International Agency for Research on Cancer, Lyon, France*
[b]*McLaughlin Centre for Population Health Risk Assessment, University of Ottawa, Ottawa, Ontario, Canada*

This paper examines the effects of systematic and random errors in recall and of selection bias in case–control studies of mobile phone use and cancer. These sensitivity analyses are based on Monte–Carlo computer simulations and were carried out within the INTERPHONE Study, an international collaborative case–control study in 13 countries. Recall error scenarios simulated plausible values of random and systematic, non-differential and differential recall errors in amount of mobile phone use reported by study subjects. Plausible values for the recall error were obtained from validation studies. Selection bias scenarios assumed varying selection probabilities for cases and controls, mobile phone users, and non-users. Where possible these selection probabilities were based on existing information from non-respondents in INTERPHONE. Simulations used exposure distributions based on existing INTERPHONE data and assumed varying levels of the true risk of brain cancer related to mobile phone use. Results suggest that random recall errors of plausible levels can lead to a large underestimation in the risk of brain cancer associated with mobile phone use. Random errors were found to have larger impact than plausible systematic errors. Differential errors in recall had very little additional impact in the presence of large random errors. Selection bias resulting from underselection of unexposed controls led to J-shaped exposure–response patterns, with risk apparently decreasing at low to moderate exposure levels. The present results, in conjunction with those of the validation studies conducted within the INTERPHONE study, will play an important role in the interpretation of existing and future case–control studies of mobile phone use and cancer risk, including the INTERPHONE study.
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Introduction

Over the last two decades, mobile telephones have come into widespread use in many countries throughout the world. The pervasive use of wireless telecommunications devices has raised concerns about the possible health effects of radio frequency fields used in mobile telephony. Recent reviews have concluded that although a number of biological effects of radio frequency fields have been identified, there is at present no clear evidence of adverse health effects (Cardis and Kilkenny, 1999; Elwood, 1999; IEGMP, 2000; British Medical Association, 2001; Krewski et al., 2001a, b, 2006; AGNIR, 2003; Habash et al., 2003; Ahlbom et al., 2004; AFSSE, 2005; Sienkiewicz and Kowalczuk, 2005).

A primary concern with mobile telephones has been the possibility of an increased risk of cancers of the brain, acoustic nerve, and salivary glands, owing to the concentration of radio frequency fields in this area occurring through the use of mobile phones. Such concerns have spawned a series of epidemiological studies focusing on the association between mobile phone use and cancer risk (Rothman et al., 1996; Dreyer et al., 1999; Hardell et al., 1999, 2000, 2001, 2002a, b, 2003a, b, 2005, 2006; Muscat et al., 2000, 2002; Inskip et al., 2001; Johansen et al., 2001; Stang et al., 2001; Auvinen et al., 2002; Christensen et al., 2004, 2005; Lönn et al., 2004, 2005; Schoemaker et al., 2005; Hepworth et al., 2006; Schüz et al., 2006). These studies have used primarily the case–control approach, with assessment of exposure relying mainly on participants' self-reports of phone use in personal interviews or postal questionnaires. Because the impact of radiofrequency exposure from mobile phones is expected to be small (if it exists) at the individual level, it is possible that biases in these studies could invalidate or complicate the interpretation of the results. Of particular concern are recall and selection biases.

Recall errors may arise from errors in an individual's reported history of use of mobile telephones, in particular from errors in the cumulative amount of phone use reported (Vrijheid et al., 2006). If such errors occur randomly, they usually bias risk estimates for dichotomous and continuous

1. Address all correspondence to: Dr. Martine Vrijheid, International Agency for Research on Cancer, 150 Cours Albert-Thomas, Cedex 08, 69372 Lyon, France. Tel.: +33+4 72 73 80 45.
Fax: +33+4 72 73 80 54.
E-mail: vrijheid@iarc.fr
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exposures and trend effects for ordered polytomous exposures towards the null (no effect). They also increase the uncertainty of risk estimates, making it more likely that real associations are not detected (Armstrong, 1998). However, for comparisons of exposure categories within polytomous exposures, bias can be in either direction (Dosemeci et al., 1990; Birkett, 1992; Dosemeci and Stewart, 1996; Armstrong, 1998). Systematic under- or overestimation of phone use leads to a bias of risk estimates upwards or downwards: if all subjects overestimate, measured relative risk estimates will be lower than the true relative risk, and vice versa. Differential recall errors in cases and controls may also lead to bias, the direction of which depends on the direction of the differences between cases and controls. A common example in epidemiological literature is one where differential recall bias occurs owing to under-reporting of exposure by control subjects or over-reporting by case subjects, producing spurious positive associations. Cases may reflect about potential causes of their disease and therefore may recall former exposures more accurately or even overestimate these exposures. Controls would tend to forget former exposures, particularly when the exposure was a long time ago. An additional possibility in brain cancer case–control studies is that cases may recall exposure less accurately, as the brain cancer may have affected their memory. The combined effects of random and systematic recall errors (which may be differential and non-differential) cannot be easily predicted.

Selection bias in case–control studies of mobile phone use may arise when selection of cases and controls into the study is related to the exposure, in the present context to the use of mobile phones. It may, for example, be envisaged that mobile phone users are more likely to agree to participate in a mobile phone study, or that they are more easily contactable than non-users. Recently, Lahkola et al. (2005) found that non-participants were less likely to use mobile phones than participants in a case–control study in Finland. On the other hand, it is also possible that mobile phone users are more mobile and therefore more difficult to contact than non-users, and therefore less likely to participate. Such selection effects will depend on the way subjects are approached to participate in the study. Participation rates tend to be higher among cases than among controls in case–control studies of mobile phone use and cancer risk (Christensen et al., 2004, 2005; Lönn et al., 2004, 2005; Schoemaker et al., 2005; Hepworth et al., 2006; Schüz et al., 2006), making selection bias a possibility.

This paper examines the effects of recall and selection bias in case–control studies of mobile phone use and cancer through sensitivity analyses based on Monte–Carlo computer simulations (Steenland and Greenland, 2004). Results from simple analytical sensitivity analyses of selection bias are also included. These sensitivity analyses have been carried out within the INTERPHONE Study, an international collaborative case–control study investigating whether mobile telephone use (specifically radio-frequency field exposure resulting from this use) is related to risk of tumors of the brain and salivary glands (Cardis and Kilkenny, 2001). Thirteen countries participate in INTERPHONE following a common protocol, making this the largest study of its kind. The assessment of the impact of possible bias is important in interpreting the findings of the INTERPHONE study, as its first results are now starting to be published (Christensen et al., 2004, 2005; Lönn et al., 2004, 2005; Schoemaker et al., 2005; Hepworth et al., 2006; Schüz et al., 2006).

Methods

The impact of recall bias was evaluated through Monte–Carlo simulation by repeated sampling from plausible recall error distributions and repeatedly estimating the odds ratio for brain cancer risk related to cumulative mobile phone use. Case–control data were generated to reproduce the relevant characteristics of the INTERPHONE study. Selection bias was introduced in the simulations by use of specified probabilities determining the probability of selection into the case–control data set for exposed and unexposed cases and controls.

Generation of Case–Control Data Set

A case–control data set was simulated in several steps. First, a large study population (175,000 subjects) was created, and each subject (denoted i) was assigned a true exposure X_i. Our simulated subjects included users and non-users of mobile phones; user status was assumed to follow a Bernoulli distribution with known probability P. Users were assigned a level of exposure (i.e., amount of phone use) by sampling from a log-normal distribution with known parameters. The user status probability P and the parameters of the log-normal exposure distribution were based on preliminary information on the distribution of exposures in controls in the INTERPHONE study. Simulated subjects whose assigned exposure was unreasonably high (higher than the maximum exposure recorded among INTERPHONE controls) were excluded. Two exposure metrics were considered: the cumulative number of calls (with risk estimates provided per 10,000 calls) and the cumulative duration of calls (with risk estimates provided per 1000 h).

Second, each study subject was assigned a probability P of disease D_i ($=1$ for a diseased and 0 for a healthy subject) according to the logistic model

$$P(D_i = 1|X_i;\, \alpha,\, \beta) = \exp(\alpha + \beta X_i)/(1 + \exp(\alpha + \beta X_i))$$

Subjects were assigned a random number U from the uniform distribution $U[0,1]$ and designated as either diseased if $U < P$ or healthy if $U \geq P$.

Third, a random sample of 1000 diseased and 2000 healthy subjects was drawn to form the simulated

case–control data set. The results of this random sample were retained as (D_i, X_i), $i = 1, \ldots, 3000$, for further analysis.

These three steps were repeated 5000 times for each of the simulation scenarios described below.

Recall Bias

Multiplicative Recall Error Model We used a multiplicative error model to describe the effects of both random and systematic recall errors. We assumed an error model of the form

$$Z = X\varepsilon$$

where X denotes the true exposure, ε denotes the multiplicative error, and Z denotes the measured level of exposure.

Information about the distribution of the multiplicative error factor ε was available from INTERPHONE validation studies in which short-term recall of volunteer subjects was compared with actual usage patterns recorded by mobile phone service providers or software-modified mobile phones (Vrijheid et al., 2006). The ratio of recalled to actual phone use followed a log-normal distribution. Estimates of the mean μ and standard deviation σ of the logarithm of this ratio are shown in Table 1. (This table is based on data from the eight countries that completed the validation study at the time this simulation study was initiated). Three sets of values of μ and σ were used in our simulation studies: the values for all countries combined were used as the most likely scenario, along with the largest and smallest values observed among these countries (as noted in Table 1).

Recall Bias Scenarios Random and systematic errors in phone use recall were considered under the following four broad recall error scenarios.

1. *Non-differential random recall error.* Under this scenario, the standard deviation σ of the measurement error distribution was varied, with the mean μ fixed at 0. Based on the results of the validation study (Table 1), the most likely values of the standard deviation were $\sigma = 0.95$ for numbers of calls and $\sigma = 1.21$ for duration of calls; extreme values were $\sigma = 0.62$ and 1.30 for number of calls, and $\sigma = 0.95$ and 1.39 for duration of calls.
2. *Non-differential recall error with systematic over- or underestimation of phone use and fixed random error.* In this scenario, the mean μ of the exposure measurement distribution was varied, while σ remained constant at the most likely value in the validation study ($\sigma = 0.95$ for number of calls, 1.21 for duration of calls). The most likely values for the mean were $\mu = -0.11$ for number of calls and $\mu = 0.37$ for duration of calls; extreme values were $\mu = -0.49$ and 0.47 for number of calls, and $\mu = 0.03$ and 0.90 for call duration (Table 1).
3. *Differential random recall error with no systematic over- or underestimation of phone use.* In this scenario, cases were subject to greater random recall error than controls, reflecting the possibility that recall of mobile phone use may be affected by their health status (i.e., the presence or absence of brain cancer). Here, μ was held constant at 0, whereas σ was assigned different values for cases and controls. In these scenarios, the value of σ for controls was set at the most likely value ($\sigma = 0.95$ for number of calls and 1.21 for duration of calls), whereas the value of this parameter for cases varied between σ and 3σ.
4. *Differential systematic over- or under-estimation of phone use and fixed random error.* In this scenario, random measurement error remained constant at the same level for both cases and controls ($\sigma = 0.95$ for number of calls and 1.21 for duration of calls), whereas the systematic error μ varied between cases and controls, and was set at $\mu = 0$ for

Table 1. Mean (μ) and standard deviation (σ) of the logarithm of the ratio of reported to actual mobile phone use from INTERPHONE validation studies (Vrijheid *et al.*, 2006).

Country	Number of calls		Duration of calls	
	Mean (μ)	SD (μ)	Mean (μ)	SD (μ)
Denmark	−0.22	0.62[a]	0.29	0.97
France	−0.10	0.95	0.37	1.15
Germany	−0.24	1.15	0.03[a]	1.38
Finland	0.07	0.78	0.43	1.12
Israel	−0.10	1.01	0.36	1.35
Italy	0.10	1.01	0.78	1.17
Sweden	−0.16	0.95	0.38	1.18
UK (SMP study)	−0.49[a]	0.84	0.06	0.95[a]
UK (operators study)	0.47[a]	1.30[a]	0.90[a]	1.39[a]
All countries combined	−0.11[a]	0.95[a]	0.37[a]	1.21[a]

[a]Values used in the simulations (minimum, maximum, and all countries combined).

controls. The three values of μ considered for cases were chosen to cover a range of effects largely based on the validation study: underestimation ($\mu = -0.49$ for number of calls and duration of calls) and overestimation ($\mu = 0.20$ and 0.47 for number of calls, and $\mu = 0.37$ and 0.90 for duration of calls). The value of $\mu = 0.20$ was chosen to reflect a scenario of moderate overestimation in cases and did not originate from the validation study.

Levels of Risk All of the above scenarios were simulated for four levels of the true odds ratio (OR) = $\exp(\beta X)$ at specified continuous levels of exposure, chosen to represent small, medium, and relatively large postulated effects. Specifically, we considered OR = 1.0, 1.1, 1.2 or 1.4 per 10,000 calls, and OR = 1.0, 1.1, 1.3, and 1.7 per 1000 h of calling time. Results with an OR of 1.0 are shown only for scenarios with differential errors between cases and controls.

Effect of Recall Bias A logistic regression model was fit to each of the 5000 simulated data sets generated under each recall bias scenario considered. The variation in the estimated odds ratios $\widehat{OR}$ across these 5000 data sets was described by calculating the average of the $\widehat{OR}s$, as well as the 2.5th and 97.5th percentiles of the distribution of $\widehat{OR}s$.

The coverage rate of the true OR was estimated by the percentage of times (out of 5000 simulations) the 95% confidence intervals around $\widehat{OR}$ contained the true OR. The accuracy of risk estimates was assessed using the relative bias (RB) in the estimated OR, defined by

$$\mathrm{RB} = 100\% \times \frac{|((|OR - 1|) - (|\mathrm{OR} - 1|))|}{(|\mathrm{OR} - 1|)}$$

where $\overline{OR}$ denotes the average of the estimated ORs $\widehat{OR}$ over the 5000 simulated data sets, OR denotes the true OR and |OR| denotes the absolute value.

Selection Bias

Calculation of Selection Bias The effect of selection bias for OR for dichotomous exposure (ever/never use of mobile phones) was calculated analytically by multiplying the true OR by a selection bias factor (Rothman & Greenland, 1998). Specifically, we have

$$\text{observed } OR = \text{true } OR * (P_{a1}P_{b0}/P_{a0}P_{b1})$$

where P_{a1} denotes the probability of selection among exposed cases, P_{a0} is the probability of selection among unexposed cases, P_{b1} is the probability of selection among exposed controls, and P_{b0} is the probability of selection among unexposed controls.

Simulation of Selection Bias The effects of selection bias on continuous exposure measures were evaluated using an adaptation of the simulation approach described above. After generating the study population and assigning exposure X_i and disease status D_i to each individual i, the selection probabilities P_{a1}, P_{b0}, P_{a0}, and P_{b1} were used to determine which individuals are selected into the case–control study. Note that the selection probabilities used in these simulations are related only to the fact of being or not a mobile phone user; they are not related to the level of mobile phone use.

In addition to estimating risk using a continuous exposure metric (per 10,000 calls), we estimated risk in four exposure categories (<50th, 50–69th, 70–90th, and >90th percentile) relative to unexposed subjects (i.e., non-users). True ORs of 1.0 and 1.2 per 10,000 calls were used for all selection bias scenarios considered. Results with an OR of 1.0 are shown only for the first, most plausible, scenario described below.

Selection Probabilities Our choice of selection probabilities was guided by preliminary results from questionnaires completed by a small sample of non-respondents in the INTERPHONE study, which provide information on the ratio of the proportion of phone users among those who participated to the proportion of users among those who did not participate in the study. All scenarios were conducted assuming three plausible participation rates among controls, respectively, 45%, 65%, and 75%. Overall, participation rate among cases was assumed to be 100%, except in one scenario where exposed cases were underselected (see below). For both cases and controls, participation rates were allowed to differ among users and non-users of mobile phones, depending on the selection bias scenario as described below.

Selection Bias Scenarios Three types of selection bias were investigated:

1. *Underselection of unexposed controls.* In this scenario, there is a higher likelihood of selecting controls who use mobile telephones than those who do not and hence mobile phone users are over-represented among controls. Assumptions underlying this first (and most plausible) scenario were based on data derived from the non-response questionnaires discussed above. The percentage of users among participating controls was set at 64%, the percentage of users among non-participating controls at 50%. Also simulated was a more extreme scenario of under-selection, with the percentage of users among non-participants set at 30%.
2. *Underselection of exposed cases*. In this scenario, there is a higher likelihood of selecting cases who do not use mobile telephones than those who do. This could occur if mobile phone among use was in fact related to disease severity. Case participation was set at 60% for users and 90% for non-users in this scenario. In the absence of existing data to guide this scenario, these percentages were based on assumed values.
3. *Underselection of exposed controls*. In this scenario, there is a higher likelihood of selecting controls who did not use

mobile phones. The percentage of users among participants was set at 64%, the percentage users among non-participants at 80%. Again, there was no existing data to base this scenario on, and these percentages were assumed values.

Results

Recall Bias

Non-differential Random Error The effects of non-differential random recall error on cancer risk estimates are summarized in Table 2 for both cumulative number of calls and call duration. For both exposure measures, the estimated OR was virtually unbiased in the case of no error. The dispersion of the sampling distribution of the estimated OR was limited; for example, 95% of the estimates obtained in the 5000 simulated samples fell in the range 1.08–1.13 when the OR = 1.1 per 10,000 calls. In the absence of recall error, coverage probabilities were close to 95% for all values of the true OR considered.

The presence of random exposure measurement error had the well-known effect of biasing the OR towards the null value of unity. For cumulative number of calls, random error of the most likely magnitude ($\sigma = 0.95$) led to a reduction in the true OR per 10,000 calls from 1.1 to 1.05, from 1.2 to 1.12 and from 1.4 to 1.24. The relative bias values shown in Table 2 demonstrate that these are reductions of between 40% and 50% in the amount the OR exceeds one. Using the most extreme σ from the validation studies ($\sigma = 1.30$), ORs were reduced to 1.02, 1.07, and 1.14, respectively, with relative biases of 66% to 77%. Coverage probabilities degraded rapidly with increasing random exposure error, with virtually none of the confidence limits encompassing the true OR when $\sigma = 0.95$ or 1.30.

The results of analyses of duration of calls were qualitatively similar to those reported above for the

Table 2. Effects of non-differential recall error on estimates of risk.

True OR	Error distribution parameters		Estimated OR			Coverage (%)	Relative bias (%)
	μ	σ	Mean	Percentiles			
				2.5th	97.5th		
Cumulative number of calls (OR per 10,000 calls)							
1.1	—	—	1.10	1.08	1.13	94.8	1.6
1.1	0	0.62	1.07	1.05	1.10	34.1	25.5
1.1	0	0.95	1.05	1.02	1.07	0.7	53.5
1.1	0	1.30	1.02	1.01	1.04	0.0	76.7
1.2	—	—	1.20	1.17	1.24	95.6	0.8
1.2	0	0.62	1.17	1.13	1.21	38.5	16.0
1.2	0	0.95	1.12	1.09	1.16	0.5	40.0
1.2	0	1.30	1.07	1.04	1.10	0.0	66.7
1.4	—	—	1.40	1.35	1.46	95.1	0.5
1.4	0	0.62	1.34	1.28	1.40	29.3	15.5
1.4	0	0.95	1.24	1.18	1.31	0.1	39.5
1.4	0	1.30	1.14	1.09	1.19	0.0	66.1
Cumulative duration of calls (OR per 1000 h)							
1.1	—	—	1.10	1.08	1.13	95.3	1.8
1.1	0	0.95	1.05	1.02	1.08	3.1	52.9
1.1	0	1.21	1.03	1.01	1.05	0.0	71.2
1.1	0	1.39	1.02	1.00	1.04	0.0	80.7
1.3	—	—	1.30	1.26	1.36	94.5	0.9
1.3	0	0.95	1.20	1.14	1.27	3.8	33.8
1.3	0	1.21	1.14	1.08	1.20	0.0	54.4
1.3	0	1.39	1.10	1.05	1.15	0.0	66.9
1.7	—	—	1.70	1.61	1.81	94.8	0.7
1.7	0	0.95	1.44	1.33	1.57	0.6	37.4
1.7	0	1.21	1.30	1.20	1.41	0.0	57.7
1.7	0	1.39	1.21	1.12	1.30	0.0	70.0

cumulative number of calls (Table 2). However, as call duration exhibited greater random error than did the number of calls, the attenuation of risk estimates towards the null hypothesis was greater than that using cumulative number of calls as the exposure metric. For example, for the largest value of $\sigma = 1.39$, the average OR was estimated to be 1.21, notably lower than the true OR of 1.7. This corresponds to a relative bias of close to 70%.

Non-differential Systematic Error The effects of non-differential systematic recall error are shown in Table 3, in the presence of a fixed level of random error. The mean μ of the error distribution for cumulative number of calls varied, on the log-scale, between −0.49, −0.11, and 0.47, translating to 39% underestimation, 10% underestimation, and 60% overestimation of exposures, respectively, when values were antilogged. As expected, underestimation of number of calls increased ORs, whereas overestimation decreased the ORs. Changes in the OR are relatively small compared to the changes found in Table 2 with the introduction of random error only. For example, for the true OR of 1.2 per 10,000 calls, the estimated OR varied from 1.20 with

Table 3. Effects of non-differential systematic recall error on estimates of risk.

True OR	Error distribution parameters		Estimated OR			Coverage (%)	Relative bias (%)
	μ	σ	Mean	Percentiles			
				2.5th	97.5th		
Cumulative number of calls (OR per 10,000 calls)							
1.1	—	—	1.10	1.08	1.13	95.8	1.6
1.1	−0.49	0.95	1.08	1.04	1.12	52.3	21.6
1.1	−0.11	0.95	1.05	1.03	1.08	3.1	47.7
1.1	0.47	0.95	1.03	1.02	1.04	0.0	70.9
1.2	—	—	1.20	1.17	1.24	95.3	0.9
1.2	−0.49	0.95	1.20	1.15	1.27	72.0	2.1
1.2	−0.11	0.95	1.14	1.10	1.18	5.1	32.4
1.2	0.47	0.95	1.07	1.05	1.10	0.0	63.4
1.2	—	—	1.20	1.17	1.24	95.3	0.7
1.2	−0.49	0.1	1.35	1.30	1.41	0.0	74.0
1.2	−0.11	0.1	1.23	1.19	1.27	75.2	13.2
1.2	0.47	0.1	1.12	1.10	1.14	0.0	39.3
1.4	—	—	1.40	1.35	1.46	95.1	0.7
1.4	−0.49	0.95	1.42	1.32	1.55	66.1	5.9
1.4	−0.11	0.95	1.27	1.21	1.35	2.1	31.7
1.4	0.47	0.95	1.14	1.11	1.18	0.0	63.9
Cumulative duration of calls (OR per 1000 h)							
1.1	—	—	1.10	1.07	1.13	95.1	1.4
1.1	0.03	1.21	1.03	1.01	1.05	0.0	72.1
1.1	0.37	1.21	1.02	1.01	1.04	0.0	80.1
1.1	0.90	1.21	1.01	1.00	1.02	0.0	88.4
1.3	—	—	1.30	1.26	1.36	95.2	1.1
1.3	0.03	1.21	1.13	1.08	1.19	0.0	55.4
1.3	0.37	1.21	1.09	1.06	1.13	0.0	68.9
1.3	0.90	1.21	1.05	1.03	1.08	0.0	82.1
1.3	—	—	1.30	1.26	1.36	94.8	0.9
1.3	0.03	0.1	1.29	1.25	1.35	91.8	2.6
1.3	0.37	0.1	1.20	1.17	1.24	0.2	33.2
1.3	0.90	0.1	1.11	1.10	1.13	0.0	62.3
1.7	—	—	1.71	1.61	1.81	95.3	0.7
1.7	0.03	1.21	1.29	1.19	1.39	0.0	59.1
1.7	0.37	1.21	1.20	1.13	1.27	0.0	72.0
1.7	0.90	1.21	1.11	1.07	1.15	0.0	84.2

underestimation to 1.07 with overestimation. The corresponding relative bias ranged from 2.1% to 63%. For true ORs of 1.1 and 1.4 per 10,000 calls, similar conclusions can be drawn. Also shown is a scenario with a much smaller (but probably unrealistic) ($\sigma = 0.1$). In this case, the effect of changing μ is more pronounced: if subjects underestimate number of calls ($\mu = -0.49$), the OR increases from 1.2 to 1.35; if subjects overestimate number of calls ($\mu = 0.47$), the OR decreases from 1.2 to 1.12.

Results for cumulative call duration were again similar to those for cumulative number of calls. Attenuation towards the null was again greater because of greater levels of overestimation of exposure modeled. In all scenarios, the relative bias is between 70% and 80% with the most likely value of overestimation, and reaches 88% when the largest overestimation error is modeled.

Differential Random Error Differential random error between cases and controls appears to have a small impact on the risk estimates (Table 4). For a true OR of 1.0, a slight upwards bias of the estimated OR is observed, with the OR increasing to 1.03 when cases are assigned a three times larger

Table 4. Effects of differential random recall error on estimates of risk.

True OR	Error distribution parameters				Estimated ORs			Coverage (%)	Relative bias (%)
	$\mu_{control}$	$\sigma_{control}$	μ_{case}	σ_{case}	Mean	Percentiles 2.5th	Percentiles 97.5th		
Cumulative number of calls (OR per 10,000 calls)									
1.0	—	—	—	—	1.00	0.96	1.03	95.2	—
1.0	0	0.95	0	0.95	1.00	0.98	1.01	96.8	—
1.0	0	0.95	0	1.90	1.02	1.01	1.04	2.7	—
1.0	0	0.95	0	2.85	1.03	1.02	1.05	0.0	—
1.1	—	—	—	—	1.10	1.08	1.13	94.9	1.2
1.1	0	0.95	0	0.95	1.05	1.02	1.07	0.7	53.5
1.1	0	0.95	0	1.90	1.05	1.03	1.07	0.9	52.2
1.1	0	0.95	0	2.85	1.05	1.03	1.07	0.9	50.2
1.2	—	—	—	—	1.20	1.17	1.24	95.1	1.0
1.2	0	0.95	0	0.95	1.12	1.09	1.16	0.5	40.0
1.2	0	0.95	0	1.90	1.10	1.07	1.14	0.1	48.1
1.2	0	0.95	0	2.85	1.09	1.06	1.13	0.0	54.4
1.4	—	—	—	—	1.40	1.35	1.46	94.9	0.6
1.4	0	0.95	0	0.95	1.24	1.18	1.31	0.1	39.5
1.4	0	0.95	0	1.90	1.20	1.14	1.26	0.0	50.3
1.4	0	0.95	0	2.85	1.16	1.11	1.22	0.0	59.2
Cumulative duration of calls (OR per 1000 h)									
1.0	–	–	–	–	1.00	0.96	1.04	95.5	—
1.0	0	1.21	0	1.21	1.00	0.98	1.01	97.5	—
1.0	0	1.21	0	2.42	1.02	1.00	1.04	3.0	—
1.0	0	1.21	0	3.63	1.03	1.01	1.05	0.2	—
1.1	–	–	–	–	1.10	1.08	1.14	95.1	2.2
1.1	0	1.21	0	1.21	1.03	1.01	1.05	0.0	71.2
1.1	0	1.21	0	2.42	1.03	1.01	1.06	0.2	66.2
1.1	0	1.21	0	3.63	1.04	1.01	1.06	0.2	62.8
1.3	—	—	—	—	1.30	1.26	1.36	94.7	0.9
1.3	0	1.21	0	1.21	1.14	1.08	1.20	0.0	54.4
1.3	0	1.21	0	2.42	1.11	1.06	1.16	0.0	63.5
1.3	0	1.21	0	3.63	1.09	1.03	1.14	0.0	70.0
1.7	—	—	—	—	1.70	1.61	1.81	95.0	0.7
1.7	0	1.21	0	1.21	1.30	1.20	1.41	0.0	57.7
1.7	0	1.21	0	2.42	1.22	1.13	1.31	0.0	69.0
1.7	0	1.21	0	3.63	1.16	1.08	1.24	0.0	76.5

random error than controls. For ORs greater than 1.0, the bias is towards the null value. This bias increases slightly with increasing differential random error when true ORs are greater than 1.1. For example, the true OR of 1.2 per 10,000 calls decreases from 1.12 when cases and controls have the same random error to 1.09 when the random error in cases is three times that in controls. The corresponding relative bias in the OR increased to a maximum of 60% for number of calls and 76% for duration of calls for the largest random error in cases.

Differential Systematic Error The effects of differences in systematic recall error between cases and controls are shown in Table 5. Random error is held at a constant level among cases and controls. Although controls are not subject to systematic exposure measurement error, cases are subject to underestimation or overestimation of exposure. Results of these scenarios show that the effect of varying the systematic bias (μ) in cases is very small compared to the effect of the large random error (σ) that exists for both cases and controls. Estimated ORs and relative bias show very little variation,

Table 5. Effects of differential systematic recall error on estimates of risk.

True OR	Error distribution parameters				Estimated ORs			Coverage (%)	Relative bias (%)
	$\mu_{control}$	$\sigma_{control}$	μ_{case}	σ_{case}	Mean	Percentiles 2.5th	Percentiles 97.5th		
Cumulative number of calls (OR per 10,000 calls)									
1.0	—	—	—	—	1.00	0.97	1.03	95.6	—
1.0	0	0.95	−0.49	0.95	0.97	0.92	1.00	38.8	—
1.0	0	0.95	0.20	0.95	1.01	0.99	1.02	84.8	—
1.0	0	0.95	0.47	0.95	1.02	1.00	1.04	40.7	—
1.1	—	—	—	—	1.10	1.08	1.13	94.8	1.2
1.1	0	0.95	−0.49	0.95	1.04	1.02	1.06	0.1	64.7
1.1	0	0.95	0.20	0.95	1.05	1.03	1.08	1.5	49.2
1.1	0	0.95	0.47	0.95	1.06	1.03	1.08	4.0	44.1
1.2	—	—	—	—	1.20	1.17	1.24	95.3	0.9
1.2	0	0.95	−0.49	0.95	1.12	1.08	1.16	0.5	41.3
1.2	0	0.95	0.20	0.95	1.12	1.09	1.16	0.6	40.3
1.2	0	0.95	0.47	0.95	1.12	1.09	1.16	0.3	41.1
1.4	—	—	—	—	1.40	1.35	1.46	95.0	0.6
1.4	0	0.95	−0.49	0.95	1.25	1.18	1.32	0.4	37.9
1.4	0	0.95	0.20	0.95	1.24	1.18	1.30	0.0	41.2
1.4	0	0.95	0.47	0.95	1.23	1.17	1.29	0.0	43.4
Cumulative duration of calls (OR per 1000 h)									
1.0	—	—	—	—	1.00	0.96	1.04	95.9	—
1.0	0	1.21	−0.50	1.21	0.98	0.93	1.00	64.7	—
1.0	0	1.21	0.37	1.21	1.01	1.00	1.02	78.8	—
1.0	0	1.21	0.90	1.21	1.02	1.00	1.04	18.0	—
1.1	—	—	—–	–—	1.10	1.08	1.14	95.2	2.0
1.1	0	1.21	−0.50	1.21	1.02	1.00	1.04	0.0	79.8
1.1	0	1.21	0.37	1.21	1.03	1.01	1.06	0.1	65.3
1.1	0	1.21	0.90	1.21	1.04	1.02	1.08	1.6	57.3
1.3	—	—	—	—	1.30	1.26	1.36	95.3	0.9
1.3	0	1.21	−0.50	1.21	1.14	1.08	1.20	0.1	54.7
1.3	0	1.21	0.37	1.21	1.14	1.08	1.19	0.0	54.7
1.3	0	1.21	0.90	1.21	1.13	1.08	1.18	0.0	56.9
1.7	—	—	—	—	1.71	1.61	1.81	94.7	0.8
1.7	0	1.21	−0.50	1.21	1.30	1.19	1.42	0.0	57.5
1.7	0	1.21	0.37	1.21	1.29	1.19	1.39	0.0	59.2
1.7	0	1.21	0.90	1.21	1.26	1.18	1.35	0.0	62.4

whether cases under- or overestimated their phone use. The most important effect continues to be the bias in risk estimates towards the null hypothesis induced by the presence of random error when the true OR is greater than 1.0. For a true OR of 1, the observed OR varies from a slight decrease (OR = 0.97 for number of calls and 0.98 for duration of calls) to a slight increase (1.02 for both).

Selection Bias Table 6 shows ORs for dichotomous exposure (ever/never use of mobile phones) corrected for selection bias. In the first scenario (underselection of unexposed controls), the true OR of 1.2 is reduced to values between 0.87 and 1.03, depending on the level of participation of controls. Even at the highest participation rate of 75% among controls, the OR is reduced from 1.2 to 1.03. More extreme underselection of unexposed controls gives measured ORs between 0.56 and 0.85. In the scenario with the same underselection of unexposed controls as in the first scenario, but with underselection of exposed cases, the reduction in the OR due to selection bias is even more pronounced. In the last scenario (underselection of exposed controls), the OR is notably increased, particularly when the participation rate among controls is only 45% (measured OR = 1.80).

As the selection bias factor in Table 6 is independent of the true OR, the measured OR can be calculated by multiplying any other value of the true OR by the selection bias factor. For a true OR of 1 therefore, the measured OR will be equal to the selection bias factors shown in Table 6.

Table 7 summarizes the effect of different selection bias scenarios on ORs for continuous exposure and those for exposure categories. The true OR for continuous exposure of 1.2 per 10,000 calls changes relatively little when selection bias is introduced. The most extreme scenario of under-selection of unexposed controls combined with a low, 45%, participation rate in controls reduces the OR to 1.16. In all other scenarios, OR estimates are closer to the true value of 1.2. Estimates of the OR in categories of exposure compared to the baseline of non-users, however, show more clearly the effects of selection bias on the shape of the exposure–response relationship. For all scenarios in which users are more likely to participate than non-users among controls, the exposure–response relationship becomes J-shaped when selection bias is introduced: ORs for all categories of exposure are reduced and the ORs for lower exposures (below the 90th percentile) are almost all below 1. For example, the first, and least extreme, scenario gives ORs of 0.74, 0.79, 0.93, and 7.18, respectively, in the four exposure categories when the participation rate is 45% (Table 7, Figure 1). This compares to values of 1.02, 1.10, 1.30, and 9.88 when there is no selection bias. Qualitatively similar results were obtained with more extreme underselection of unexposed controls, and when overselection of exposed controls is combined with under-representation of exposed cases (Table 7). The OR for

Table 6. Impact of selection bias on ORs for dichotomous exposure (user/non-user) — analytical correction.

True OR	Participation rate controls (%)	Probability of selection				Selection bias factor	Measured OR
		Cases		Controls			
		Users (a)	Non-users (b)	Users (c)	Non-users (d)	= a*d/b*c	= true OR*bias
Underselection of unexposed controls[a]							
1.2	45	1	1	0.51	0.37	0.73	0.87
1.2	65	1	1	0.70	0.57	0.81	0.98
1.2	75	1	1	0.79	0.68	0.86	1.03
Extreme underselection of unexposed controls[b]							
1.2	45	1	1	0.64	0.30	0.47	0.56
1.2	65	1	1	0.80	0.49	0.61	0.74
1.2	75	1	1	0.86	0.61	0.71	0.85
Underselection of exposed cases and underselection of unexposed controls[a]							
1.2	45	0.6	0.9	0.51	0.37	0.48	0.58
1.2	65	0.6	0.9	0.70	0.57	0.54	0.65
1.2	75	0.6	0.9	0.79	0.68	0.57	0.69
Underselection of exposed controls[c]							
1.2	45	1	1	0.40	0.60	1.50	1.80
1.2	65	1	1	0.60	0.77	1.28	1.54
1.2	75	1	1	0.71	0.84	1.18	1.42

[a]Based on 64% users among respondents, 50% among non-respondents.
[b]Based on 64% users among respondents, 30% among non-respondents.
[c]Based on 64% users among respondents, 80% among non-respondents.

Table 7. Impact of selection bias on ORs for continuous and categorical exposure — simulation results.

True OR	Participation rate controls (%)	Probability of selection				Measured OR (2.5–97.5th percentile range)				
		Cases		Controls		OR per 10,000 calls	Categorical OR compared to baseline (non-users)[a]			
		Users	*Non-users*	*Users*	*Non-users*		0–50th %	50–70th %	70–90th %	>90th %
No selection bias										
1.2	100	1	1	1	1	1.20 (1.18–1.23)	1.02 (0.87–1.22)	1.10 (0.78–1.44)	1.30 (0.94–1.66)	9.88 (7.46–13.12)
Underselection of unexposed controls[b]										
1.2	45	1	1	0.51	0.37	1.18 (1.16–1.21)	0.74 (0.61–0.91)	0.79 (0.59–1.05)	0.93 (0.72–1.26)	7.18 (5.49–8.75)
1.2	65	1	1	0.70	0.57	1.19 (1.17–1.22)	0.83 (0.68–1.04)	0.90 (0.69–1.15)	1.09 (0.81–1.40)	8.23 (6.46–10.52)
1.2	75	1	1	0.79	0.68	1.20 (1.16–1.23)	0.88 (0.69–1.06)	0.95 (0.68–1.27)	1.12 (0.85–1.56)	8.73 (6.76–11.29)
Extreme underselection of unexposed controls[c]										
1.2	45	1	1	0.64	0.30	1.16 (1.14–1.20)	0.48 (0.37–0.61)	0.52 (0.37–0.68)	0.60 (0.47–0.83)	4.70 (3.38–6.63)
1.2	65	1	1	0.80	0.49	1.18 (1.15–1.22)	0.62 (0.52–0.74)	0.65 (0.50–0.83)	0.80 (0.63–1.00)	6.14 (4.69–8.38)
1.2	75	1	1	0.86	0.61	1.18 (1.16–1.22)	0.72 (0.58–0.86)	0.77 (0.59–1.08)	0.92 (0.72–1.23)	7.02 (5.55–9.07)
Underselection of exposed cases and underselection of unexposed controls[b]										
1.2	45	0.6	0.9	0.51	0.37	1.17 (1.14–1.19)	0.49 (0.38–0.57)	0.53 (0.40–0.71)	0.63 (0.49–0.81)	4.89 (3.84–6.24)
1.2	65	0.6	0.9	0.70	0.57	1.17 (1.15–1.20)	0.55 (0.44–0.69)	0.58 (0.45–0.74)	0.70 (0.51–0.95)	5.41 (4.30–6.76)
1.2	75	0.6	0.9	0.79	0.68	1.18 (1.15–1.21)	0.59 (0.48–0.71)	0.63 (0.48–0.81)	0.75 (0.56–1.01)	5.76 (4.47–6.83)
Underselection of exposed controls[d]										
1.2	45	1	1	0.40	0.60	1.22 (1.19–1.26)	1.57 (1.26–1.93)	1.63 (1.28–2.14)	2.00 (1.56–2.54)	15.39 (12.00–20.74)
1.2	65	1	1	0.60	0.77	1.21 (1.18–1.24)	1.31 (1.06–1.55)	1.38 (1.03–1.75)	1.67 (1.16–2.16)	12.98 (9.42–18.39)
1.2	75	1	1	0.71	0.84	1.21 (1.18–1.24)	1.22 (0.96–1.49)	1.31 (0.92–1.69)	1.54 (1.15–1.97)	11.82 (9.39–14.24)
Underselection of unexposed controls[b]										
1.0	45	1	1	0.51	0.37	0.99 (0.94–1.01)	0.72 (0.59–0.85)	0.73 (0.55–0.92)	0.72 (0.56–0.90)	0.75 (0.50–1.02)
1.0	65	1	1	0.70	0.57	0.99 (0.95–1.02)	0.82 (0.68–0.95)	0.82 (0.62–1.02)	0.81 (0.66–1.10)	0.82 (0.62–1.13)
1.0	75	1	1	0.79	0.68	0.99 (0.96–1.03)	0.87 (0.74–1.05)	0.87 (0.67–1.09)	0.87 (0.68–1.12)	0.85 (0.62–1.23)

[a]Categories defined by percentiles of the exposure distribution.
[b]Based on 64% users among participants, 50% among non-participants.
[c]Based on 64% users among participants, 30% among non-participants.
[d]Based on 64% users among participants, 80% among non-participants.

the highest exposure category (>90th percentile) is never reduced below 4.7 (in the scenario of extreme underselection of unexposed controls), with the 2.5th percentile never falling below 1. The ORs increase when exposed controls are underselected; these effects are again more pronounced for categorical as compared to continuous exposures (Table 7).

Selection bias has a much greater effect on risk estimates based on categorical exposures than those based on continuous exposures, presumably because of the dominant effect of highly exposed individuals in estimating the slope of the exposure–response curve in the latter case. This positive slope is maintained even though the ORs are less than unity in the lower exposure categories.

Table 7 also shows the results of simulations with a true OR of 1.0, under the most likely scenario of underselection of unexposed controls. As expected, all the categorical ORs within one scenario are reduced by the same factor with no apparent exposure–response relationship.

Discussion

Case–control studies of mobile phones and cancer risk can be subject to recall bias and uncertainty due to inaccurate recall of mobile phone use by the study subjects, and to selection bias related to non-participation. In this article, we have evaluated the possible effects of errors in recall and of selection bias on estimates of risk in such studies. These sensitivity analyses were based, where possible, on plausible assumptions on levels of error from existing validation studies and from non-response questionnaires, and therefore give realistic indications of the direction and magnitude of possible bias in such studies.

Recall Bias

Our results suggest that plausible levels of non-differential random errors in the recall of amount of phone use can lead to substantial underestimation of cancer risk associated with mobile phone use when the true OR is greater than 1.0.

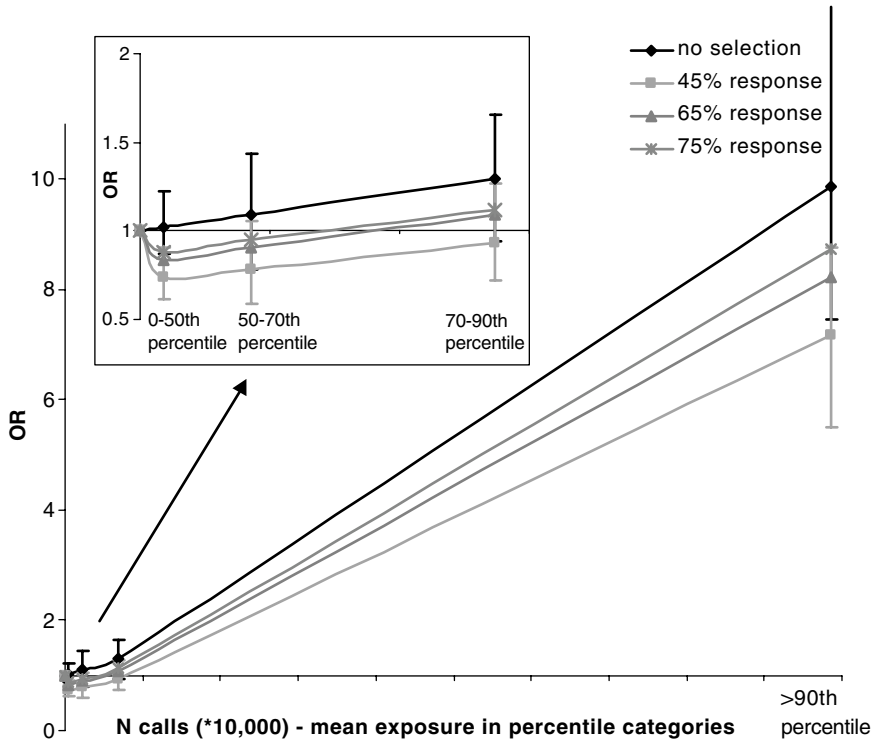

Figure 1. J-shaped exposure–response relationship in the case of underselection of unexposed controls, based on 64% users among participants, 50% among non-participants. (see Table 7 for values of the ORs).

Reductions of up to 30% in the OR estimate are seen in the most extreme scenarios with only random error. Further, the findings indicate that these random errors can have a greater impact on risk estimates than plausible levels of non-differential systematic error. Our results also show that bias due to differential levels of under- or overestimation of phone use by cases and controls is very small compared to the bias owing to the levels of random error simulated. In fact, the estimated ORs varied very little depending on whether cases under- or overestimated their amount of phone use, even though a relatively wide range of values was modeled. The net effect of combining non-differential random error and differential recall bias was still to substantially reduce the estimated OR. Our simulation results also indicate that, when the true OR is 1.0, differential random error can lead to small spurious associations between exposure and outcome when the random error among cases is much greater than among controls.

It has previously been documented in sensitivity analyses of dichotomous exposures that even large differences in the accuracy of recall between cases and controls may have only minor impact on the results of a study (Drews and Greenland, 1990), and that differential recall bias may not always give upwardly biased results (Greenland, 1996). These results are similar to those found in the present analysis of differential systematic error with a continuous exposure metric.

Validation studies carried out as part of INTERPHONE provided the prior plausible distributions of random and systematic recall errors used in the simulations. These validation studies used volunteer subjects, evaluated only short-term (6 months) recall, and did not provide information on possible differential recall between cases and controls (Vrijheid et al., 2006). Errors in long-term recall of case–control study subjects may be larger than those measured short-term in the volunteer study. However, scenarios of extreme recall errors, taken from the most extreme country-specific results of the validation study, were modeled so that a range of errors could be evaluated. These validation studies did not provide any information about possible differences in recall between cases and controls. There are examples in epidemiological studies where recall bias occurs owing to under-reporting of exposure by control subjects or over-reporting by case subjects. It is not self-evident that this is the case in studies of brain cancer risk and mobile phone use: brain cancer cases may, owing to their condition, recall less phone use or recall their use less accurately than controls. The validation studies showed a tendency for volunteers to underestimate the number of phone calls they made, but to overestimate the duration of phone calls (Vrijheid et al., 2006). As a consequence, the direction of any bias may also depend on the exposure metric used. In any case, the scenarios modeled showed very little impact of differential recall bias in the presence of the substantial random error.

Even when cases overestimated call duration by a factor of 2.5 and the controls did not overestimate or underestimate call duration, the OR for a continuous exposure hardly changed. This indicates that very extreme levels of differential systematic bias would be needed to substantially change the risk estimates for continuous exposure in this type of study.

As part of INTERPHONE, historical billing records of case–control subjects are being collected from phone service providers in a few participating countries to provide information on the possibility of differential recall between brain tumor cases and healthy controls. These data will provide important additional information on the plausibility of the differential recall bias scenarios modeled in the current sensitivity analyses.

Selection bias

Our results suggest that selection bias resulting from differential participation in the study by exposed and non-exposed cases and controls can lead to J-shaped exposure–response patterns when the true OR is greater than 1.0, with risk apparently decreasing at low to moderate exposure levels. In the most recent studies, including significant numbers of long-term users, ORs below unity have been reported (cf. Christensen et al., 2005; Lönn et al., 2005; Schoemaker et al., 2005, Hepworth et al., 2006, Schüz et al., 2006). This could be explained by selection bias, as observed in our simulations. These studies categorized exposure into quartiles and given the very skewed distribution of exposure of mobile phone use, it is possible that an increase such as that seen in our simulations only in the highest decile could have been missed.

The effect of the selection bias depends on the participation rates and on the distribution of exposure between participants and non-participants. The mobile phone use rates among participating and non-participating controls in our sensitivity analyses were based on data from non-response questionnaires from the INTERPHONE study. For cases we assumed two different scenarios, one where participants and non-participants were equally likely to use mobile phones, and one where mobile phone use was more likely among non-participants. The scenario where mobile phone use rates in participating and non-participating cases are identical to those in participating and non-participating controls was not modeled, as this would not lead to selection bias. In the Finnish study by Lahkola et al. (2005), mobile phone use was higher among participants than among non-participants. However, the difference in mobile phone use rates between participants and non-participants was similar among cases and controls, and did not lead to substantial bias in estimates of risk. The scenarios modeled in the present paper are more extreme than either of these two situations, and may therefore lead to greater bias than may be observed in practice. Further, we only modeled scenarios where selection into the study was related to whether or not the subject was a mobile phone user, not to the amount of phone use. Refinements of the current sensitivity analyses, using selection probabilities that depend on the amount of use, could be envisaged.

Limitations

Although we have attempted to base our simulations on conditions that may be encountered in practice, our findings should only be considered as indicative as we have had to make some assumptions about the underlying recall and selection bias models. Nonetheless, we believe that the present findings are realistic and will be of value in guiding the interpretation of the forthcoming INTERPHONE study results.

Confidence limits on the OR for cancer in relation to mobile phone use were relatively narrow in our simulation study. This occurs for three reasons. First, the data are generated under a perfectly specified logistic regression model, and analysed using this same model. Second, while the model takes into account interindividual variation in cancer risk, it is assumed that mobile phone use is the only covariate affecting individual risk. In practice, additional covariates, such as lifestyle, environmental, and genetic risk factors, will also determine individual cancer risk. Third, risk estimates based on the estimated slope of the exposure–response relationship using an essentially continuous exposure measure such as cumulative number of calls or cumulative call duration (representing the majority of estimates considered in this article) can be expected to demonstrate less uncertainty than risk estimates calculated within specific categories of exposure. Because the confidence limits were narrow, the lower confidence limit on the true OR almost always exceeded the null value of unity, resulting in virtually 100% power for detecting even the lowest postulated elevated OR of 1.1 regardless of the magnitude of random error. Because additional variability is expected in real data sets, the impact of the both random and systematic errors on statistical power to detect an increased risk is not clear. It is unlikely, however, that the power would remain as high as observed in these simulations.

Correcting for Recall Bias

If the degree of random and systematic recall error can be estimated with reasonable accuracy, it is possible to adjust for the presence of such error using statistical techniques such as regression calibration or simulation extrapolation (Fung and Krewski, 1999a, b; Mallick et al., 2002; Carroll et al., 1995). Such adjustments have been made in recent case–control studies of the association between residential radon exposure and lung cancer risk (Darby et al., 2005). Using the results of the present study as a guide, supplementary analyses will be carried out in INTERPHONE adjusting for measurement error and results compared with those of the main unadjusted analyses.

Conclusions

In conclusion, the analyses reported in this paper demonstrate the effects of both recall and selection bias in case–control studies of mobile phone use and cancer. The present results, in conjunction with those of the validation studies conducted within the INTERPHONE study, will play an important role in the interpretation of existing and future case–control studies of mobile phone use and cancer risk, including the INTERPHONE study.

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D Krewski is the NSERC/SSHRC/McLaughlin Chair in Population Health Risk Assessment at the University of Ottawa, and a Visiting Scientist at the International Agency for Research on Cancer.

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