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Subject response rates in case-control studies of cancer: time trends, study design determinants, and quality of reporting

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Ce mémoire intitulé:

Subject response rates in case-control studies of cancer: time trends, study design determinants, and quality of reporting

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Résumé

Objectifs: Examiner les tendances temporelles, les déterminants en lien avec le design des études et la qualité des taux de réponse rapportés dans des études cas-témoins sur le cancer publiées lors des 30 dernières années.

Méthodes: Une revue des études cas-témoins sur le cancer a été menée. Les critères d'inclusion étaient la publication (i) dans l'un de 15 grands périodiques ciblés et (ii) lors de quatre périodes de publication (1984-1986, 1995, 2005 et 2013) couvrant trois décennies. 370 études ont été sélectionnées et examinées. La méthodologie en lien avec le recrutement des sujets et la collecte de données, les caractéristiques de la population, les taux de participation et les raisons de la non-participation ont été extraites de ces études. Des statistiques descriptives ont été utilisées pour résumer la qualité des taux de réponse rapportés (en fonction de la quantité d'information disponible), les tendances temporelles et les déterminants des taux de réponse; des modèles de régression linéaire ont été utilisés pour analyser les tendances temporelles et les déterminants des taux de participation.

Résultats: Dans l'ensemble, les qualités des taux de réponse rapportés et des raisons de non-participation étaient très faible, particulièrement chez les témoins. La participation a diminué au cours des 30 dernières années, et cette baisse est plus marquée dans les études menées après 2000. Lorsque l'on compare les taux de réponse dans les études récentes a ceux des études menées au cours de 1971 à 1980, il y a une plus grande baisse chez les témoins sélectionnés en population générale (-17,04%, IC 95%: -23,17%, -10,91%) que chez les cas (-5,99%, IC 95%: -11,50%, -0,48%). Les déterminants statistiquement significatifs du taux de réponse chez les cas étaient: le type de cancer examiné, la localisation géographique de la population de l'étude, et le

mode de collecte des données. Le seul déterminant statistiquement significatif du taux de réponse chez les témoins hospitaliers était leur localisation géographique. Le seul déterminant statistiquement significatif du taux de participation chez les témoins sélectionnés en population générale était le type de répondant (sujet uniquement ou accompagné d'une tierce personne).

Conclusion: Le taux de participation dans les études cas-témoins sur le cancer semble avoir diminué au cours des 30 dernières années et cette baisse serait plus marquée dans les études récentes. Afin d'évaluer le niveau réel de non-participation et ses déterminants, ainsi que l'impact de la non-participation sur la validité des études, il est nécessaire que les études publiées utilisent une approche normalisée pour calculer leurs taux de participation et qu'elles rapportent ceux-ci de façon transparente.

Mots clés: épidémiologie, méthodes épidémiologiques; études cas-témoins; cancer, taux de participation; taux de réponse, collecte de données

Abstract

Objectives: To examine the time trends, study design determinants, and quality of reporting of response rates in published case-control studies of cancer over the past 30 years.

Methods: A review was conducted of case-control studies of cancer. Inclusion criteria required publications in 15 major journals, during four publication periods spanning three decades (1984-86, 1995, 2005 and 2013). 370 studies were selected and reviewed. Information on study base ascertainment, data collection methods, population characteristics, response rates, and reasons for non-participation was extracted. Quality of response rate reporting was assessed based on the amount of information reported. Descriptive statistics were used to summarize the quality of the reporting, time trends and the determinants of response rates; linear regression models were used to analyse time trends and determinants of response rates.

Results: Overall, the quality of reporting of response rates and reasons for non-participation was very poor, especially for control series. Participation has declined over the past 30 years, and this decline was steeper in studies conducted after 2000. When comparing the response rates in recent studies to that in studies conducted during 1971-1980, there was a greater decline of this rate in population controls (-17.04%, 95% CI: -23.17%, -10.91%) than in cases (-5.99%, 95% CI: -11.50%, -0.48%). Statistically significant determinants of response rates among cases were: cancer type examined, location of the study population, and mode of data collection. The only statistically significant determinant of response rates among medical source controls was location of the study population. The only statistically significant determinant of response rates among population controls was type of respondent (self only or self and proxy) accepted by studies.

Conclusion: Response rates in case-control studies of cancer seem to have declined and this decline has accelerated in recent studies. In order to appreciate the true level of non-participation and its determinants, as well as the impact of non-participation on validity of studies, there is a need for more transparent reporting and standardized calculation of response rates in published studies.

Key words: epidemiology, epidemiologic methods; case-control studies; cancer, response rate; participation rate, data collection

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List of abbreviations

95% CI	95% Confidence Interval
OR	Odds ratio
SPSS	Statistical Package for the Social Sciences
CEBP	Cancer Epidemiology, Biomarkers & Prevention
AJE	American Journal of Epidemiology
CCC	Cancer Causes & Control
IJC	International Journal of Cancer
SES	Socioeconomic Status

I dedicate this dissertation in loving memory of my father, who lost his life to stomach cancer in 2011. He inspired me to be a brave, determined and caring person. I am forever grateful to him for the love he had provided me and for shaping me into who I am today.

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1 Introduction

1.1 Case-control study design and its application for cancer research

A dictionary of epidemiology (1) defines the case-control study as a study design which classifies people based on a disease outcome where the cases have the disease of interest, and in which a suitable control group consists of people without the disease. The relationship of an exposure to the disease of interest is examined by comparing cases and controls with regard to frequency of exposure or, levels of the exposure, in each group (1).

This design is one of the most utilized types of study design in analytical epidemiological research, and has contributed greatly in improving our understanding of the etiology of many diseases with great public health importance (2-4). The first recognized modern case-control study was conducted in 1926 by a British physician named Lane-Claypon to study the role of reproductive experience in the etiology of breast cancer (5). It wasn't until the 1950s that this design, referred to at the time as a "retrospective study", became more widely used (2, 6, 7). The increasing interest in this method was partly attributable to its successful implementation in four influential case-control studies which established the causal relationship between cigarette smoking and lung cancer (8-11). Indeed, this design is particularly useful to study cancer etiology because cancer is a rare disease with a long induction period. Adopting this design permits researchers to enroll a sufficient number of cancer patients within a relatively short period of time, thus economizing time and maximizing efficiency (3, 4, 12).

1.2 Control selection in case-control studies

In case-control studies, the primary goal for control selection is to ensure a representative covariate distribution in selected controls to that of the source population of cases (3) (13). Wacholder et al (13) proposed three comparability principles to minimize bias in control selection. The first is the principle of study base, in which cases and controls should come from the same source population; the second is the principle of deconfounding, in which the confounding factors should not be allowed to distort the estimation of risk under study, and the third is the principle of comparable accuracy, in which the degree of accuracy in exposure measurement should be equivalent for cases and controls. Common types of controls employed by epidemiologists include population-based and medical-source-based controls (3). Some common fallacies in control selection could include restrictions to only controls at risk of exposure of interest, or to only controls that are healthy (3).

1.3 Non-response bias in case-control study design

The primary concern of an epidemiologic study is to ensure the validity of the estimate of association between an exposure and a disease (3). The validity of this estimate could be compromised due to a selection bias, which occurs when there is a distortion in the sampling frame or in the procedures used to select subjects or in factors that influence study participation (3). Non-response bias is a type of selection bias in survey-based case-control studies where the probability of subject participation differs by exposure level and by disease outcome or by factors associated to them (14). Response rates have often been used as an indicator to estimate a study's potential for non-response bias; the lower the rates, the higher the chance that participants do not accurately represent the target population, hence increasing the chance of

producing biased risk estimates of association (14, 15). It is believed that subject participation in epidemiologic studies has declined over the past decades (14) and that this decline is steeper in controls than in cases (16), which increases a case-control study's potential for non-response bias.

1.4 Definition of "response rate"

It would make little sense to compare response rates between different case-control studies if each study defined, calculated and reported response rates differently (14, 15, 17, 18). In other words, a response rate cannot be interpreted if no explanation is provided to explain its meaning. The lack of explanation would not only increase the reader's chance of misinterpreting the validity of the reported results, but would also make it impossible to properly compare response rates provided by different studies (19, 20). Indeed, this is one of the major problems with the study of response rates. The term "response rate" (theoretically, it should be better addressed as "response proportion") has been defined in different ways, and is often used interchangeably with other terms such as "participation rate" and "cooperation rate" (14). Appendix 1 provides several examples of the definitions of response rate, cooperation rate and participation rate.

In practice, the ambiguity of the definition of response rates often lies in the choice of denominator for its calculation (14, 18). In addition, the definition and calculation of response rate differ depending on the study design selected. Although there is no official rule defining how a response rate must be calculated (19), there have been suggestions made to standardize its definition and calculation.

In household telephone surveys where subject eligibility is unknown prior to being contacted, *response rate* is often calculated as the number of households who participated

divided by the total number of households selected (20). The American Association for Public Opinion Research (AAPOR) (21) and the Public Opinion Research in the Government of Canada (22, 23) provide a similar definition for response rate. They define it as the number of participants divided by the sum of the numbers of participants, nonparticipants (including refusals and noncontacts), and persons of presumed but unconfirmed eligibility (21-23) .

In epidemiologic studies, the *response rate* is defined as the number of people interviewed divided by those who were selected and eligible for the study (15, 20). For the purpose of this thesis, we are mainly interested in studying response rates in epidemiologic studies, specifically in case-control studies. Similar to social survey research, the main source of confusion regarding the definition and calculation of response rates in case-control studies, lies within the denominator, and the concept of subject eligibility (19). For example, subjects who are unable to be contacted, in poor health, or are forbidden to be contacted by their doctors, are often deemed as ineligible by researchers and are excluded from the denominator, resulting in a "response rate" that is artificially inflated (19, 20).

1.5 Impact of response rates on validity of results

If a study has low response rates and if non-respondents are different from respondents with regard to the exposure variable and disease status under study, the estimates of relative risk may be biased (3, 24). Harris et al. (25) used data from a case-control study plus simulations to assess the degree of error of observed odds ratio (OR) over the true OR when different levels of non-response bias were introduced in a sample. The level of this bias was manipulated through the inclusion of different proportions of exposed and non-exposed cases in the sample. They concluded that even a low level of non-response bias could yield a dramatic impact on the

observed OR, either inflating or attenuating the true OR. There are advanced statistical methods available to input values to replace the missing data due to nonresponse; however, such methods cannot be implemented when characteristics of the non-respondents are not missing at random, which is often the case (24).

Although it is clear in theory that studies with lower response rates have greater likelihood of nonresponse bias, the extent of such bias depends on the pattern of non-response in the four cells of the 2x2 table of cases/controls by exposed/unexposed. In practice, sometimes low overall response rates produce little bias and sometimes they produce considerable bias. (14-16, 18, 26). However, the more we know about the reasons for nonresponse, the more we can speculate about a study's likelihood of bias. Thus, it is crucial that authors provide a well-documented report of response rates (14, 18, 27). This reporting should include the efforts made to examine the presence of nonresponse bias, and if possible, the methods used to try to reduce it, so that readers can judge the validity of each study. Unfortunately, the reporting of nonresponse bias in epidemiologic studies was rarely examined. In a study that examined this issue using 81 published articles, 57% of the articles did not mention the possible effects of nonresponse bias and only 17% briefly mentioned it in the discussion (28).

1.6 Determinants of response rates

Many epidemiologists believe that it is becoming more and more challenging to obtain high response rates in epidemiologic studies (3). This could be the result of a general decrease in civic participation in scientific studies over the past years; moreover, recent epidemiologic studies have been facing increasing obstacles imposed by ethics review authorities in accessing subject(14). The main factors that have been investigated previously regarding their effects on

response rates are individual level sociodemographic characteristics such as sex, education, health or employment status (14, 16, 29), with varying results. There has been little investigation of study design factors such as subject recruitment and interview methods (3, 14).

1.7 Response rates in case-control studies of cancer

Because of to the lack of consistency and transparency in the calculation and reporting of response rates, it is difficult to properly evaluate its determinants and time trends (14, 19). Although there is evidence indicating a decline in subject response rates in epidemiologic case-control studies (14-16, 30), they all suffer from very small sample sizes and collected few data on the determinants of the response rate. Moreover, the current state of subject participation in case-control studies of cancer is unknown, as findings on this topic have not been updated for the past decade.

Therefore, it is important to establish: 1) how response rates are calculated and reported, 2) what are the typical levels of response rate seen in recent case-control studies, 3) whether there is a trend in response rates of case-control studies of cancer and, 4) what are the determinants of response rates. This thesis attempts to elucidate these issues.

2 Literature review

Search strategy

We identified and included in this review of literature pertinent publications in English through the PubMed and Google Scholar search engines, using a combination of keywords (case-control studies, epidemiologic studies, response rate, participation, cancer, questionnaire, research methods, epidemiologic methods, non-response).

2.1 Reporting of response rates

The quality of reporting for subject participation in published case-control studies was rarely evaluated. No data exists on the quality of response rate reporting in studies published in the last 10 years. However, one study published in 1995 speculated that the quality of reporting has deteriorated over time (20). One review (16) that examined this issue in 2003highlighted the general poor quality of reporting of response rates in epidemiologic studies , and concluded that 56% of case-control studies failed to report any information on response rates. One commentary published in 2012 (15) suggested that in our current era where study recruitment and data collection methods have evolved in complexity, and where subject recruitment and data collection have been facing increasing external restraints, no simple definition of response rates can be applied to all studies. Instead, studies should describe in detail the ascertainment method for the eligible study population and the methods used to contact and collect information from them. Response rates should be documented at every stage of the study and reasons for non-participation should be documented as well. If possible, characteristics of participants and nonparticipants should also be provided (15).

Although there was a lack of reporting of response rates in published studies, efforts have been made to improve the reporting quality of subject participation in epidemiologic studies. In 2007, a group of epidemiologists and survey methodologists developed a statement named *the Strengthening the Reporting of Observation Studies in Epidemiology (STROBE)* to promote detailed reporting of study methods in observational epidemiologic studies (31). This statement consists of a checklist providing guidance to authors about proper reporting for observational studies, and includes suggested methods to report response rates (31). However, the evidence of its effect on the reporting of this rate is still lacking.

2.2 Time trend of response rates

It is widely believed that subject response rates in epidemiologic studies have declined over the past decades (14); many epidemiologists believe that the rate of this decline has accelerated, and this decline is steeper for controls than cases (16). However, those concerns were often expressed in the form of commentaries or editorials, actual time trend analyses of response rates in epidemiologic studies are lacking. The few published studies (16, 20, 32-34) that examined this trend in case-control studies analyzed data in studies conducted from the 1970s to the early 2000s. No data exists on the time trend of response rates in studies conducted over the last decade.

A majority (20, 33, 34) of the previous publications (16, 20, 32-34) that examined subject response rates in case-control studies only studied subject participation in population controls. Slattery et al (20) compared the response rates of population controls recruited using the random-digit dialing method in two American cancer studies conducted in the mid-1980s to two similar studies conducted in the late 1970s or early 1980s, and reported that population controls'

response rates had declined by 16-28% during this period. Another publication (33) examined the amount of researchers' efforts needed to maintain high response rates in population controls in the United States, and concluded that the amount of effort needed to maintain high control participation nearly doubled from 1991 to 2003. Three reviews (16, 32, 34) have examined the time trends of response rates in surveyed case-control studies conducted between 1970s to the early 2000s. Two reviews examined the time trends of response rates in North American or German populations in case-control studies published from the 1980s to the 1990s, and concluded that subject response rates did not change significantly until the late 1990s. One review (16) examined time trends of response rates in case-control studies conducted from 1970 to 2003, and reported significant declines of response rates in both cases (-1.18% per year) and controls (-1.49% per year); in addition, they reported steeper but non-significant declines of response rates observed in studies conducted from 1990 to 2003.

2.3 Determinants of response rates

Given the importance of response rates in epidemiologic studies, it is essential to study its determinants. During the past three decades, there has been an observed downward trend in participation in scientific studies due to broader social reasons, which epidemiologists have no control over (14). Factors such as the emergence of telemarketing and political polls, and the population's general decrease in volunteerism in social participation all play an important role in shaping response rates (14, 15). Subjects' sociodemographic characteristics, such as sex, SES, education, health status, employment status, marital status, being exposed to the exposure of interest, and having the disease being examined, have also been shown to influence subject participation (14, 18, 29, 35-37). However, researchers have no control over the

sociodemographic characteristics of their sampled population and there was little evidence of effective strategies that can be applied to all studies to increase participation via targeting specific sociodemographic characteristics (14). Yet, certain study design factors have been shown to be associated with the probability of success in enrolling subjects in epidemiologic studies. Evidence from reviews that examined studies published prior to the mid-2000s concluded that studies contacting subjects in person had a tendency to yield higher response rates than studies using telephone or other less personal forms of contact (14, 20, 30, 38, 39). Studies using incentives, with shorter interview/questionnaire length, or involving non-invasive procedures have also been associated with higher response rates (14, 18). However, as technology and society evolve over time, it is possible that factors that influence response rates in one era play a different role in another era (15, 40, 41). In addition, as new methods for recruitment and data collection have been introduced, such as web-based questionnaire and biologic sample collection , there is an emerging need to study the impact on response rates of the use of such methods (30). Meanwhile, the enhanced scrutiny introduced by institutional review boards through privacy laws has also imposed major challenges in subject recruitment for epidemiologic studies, thus lowering subject response rates and preventing the collection of information from nonparticipants for comparison purposes (14, 25, 42-46).

2.4 Overview of evidence

Current assessments of time trends, determinants, and quality of reporting of response rates in case-control studies are lacking. Previous reviews reported inconsistency in the trends, calculation, and reporting of response rates in epidemiologic case-control studies published from the 1970s to the early 2000s. Although response rates alone do not determine the presence of

selection bias, the lack of information provided by authors on non-respondents hinders the ability of the readers to judge the validity of the study and to compare it to others. Response rates and nonresponse bias have been heavily investigated in social survey research, but analogous effort is lacking in epidemiologic studies. The few reviews that have examined these issues in case-control design all suffered from small sample sizes, and thus were unable to explore in detail the reasons for non-participation and the determinants of subject participation for each subject series. Moreover, their findings on the time trends of response rates were based on the authors' reported value of this rate. Given the inconsistency in the methods used to calculate response rates in published studies, and the rapid evolution of survey instruments used in epidemiologic studies in recent years, coupled with the changes in privacy laws imposed on researchers regarding epidemiologic research, it is timely to conduct an up-to-date review of these issues to inform the current and past levels of subject participation in case-control studies of cancer. Namely, there is a need to conduct new reviews with bigger sample sizes, adopting more rigorous definition of response rate, and providing more detailed information on potential study design determinants, to provide an updated assessment of subject response rates in case-control studies of cancer.

3 Objectives of this research

In this methodological investigation, we will examine the trends and characteristics of subject response rates in the context of questionnaire-based case-control studies of cancer. Our objectives are 1) to describe the quality of reporting of response rates in case-control studies of cancer and the evolution of reporting quality over the past 30 years, 2) to assess the current level and time trend of response rates in case-control studies of cancer, and to examine study design determinants that are associated with this rate.

4 Methods

4.1 Search strategy and Sample selection

This is a review of questionnaire-based case-control studies of cancer that were published over the past 30 years. Over this entire period there would undoubtedly have been many thousands of articles describing case-control studies of cancer. It would have been impossible to review them all individually in the context of a master's thesis. Furthermore, in an initial exploration of the usefulness of PubMed searches, we found that there was no reliable way to find all case-control studies as this was not a universally-used keyword, especially in earlier years, and even less successful was the attempt to find studies using keywords concerning response rates. The methodology we envisaged would require an in-depth review of each identified study. Given the enormous number of such studies and the practical limitation of not being able to review them all, and the impracticality of using PubMed searches for this purpose, we had to develop a strategy to restrict numbers but yet maintain relevance. Namely we decided to search all issues one-by-one of selected journals in selected years and concerning certain broad topics. This required a selection of a limited number of journals, as trying to review every journal in which a case-control study might conceivably have been reported was utterly impractical. Even when we had identified a limited number of journals, the number of articles to go through was so large that we had to select certain years of publication to keep the project feasible.

The selection of journals was based on the opinions and the records of Dr Jack Siemiatycki, and on a limited PubMed search. Dr Siemiatycki has been one of the leading cancer epidemiologists over this period of time. In addition to being a leading researcher, he was an

associate editor of journals and a frequent reviewer of manuscripts for journals and of articles for various expert panels, often for studies involving cancer epidemiology. He has amassed a personal database of cancer epidemiology articles that numbers in the thousands. He first considered and provided his opinions on which were the main journals for cancer case-control studies over this period. This was then compared with the list of citations in his extensive database of articles, and then it was compared with the PubMed search we carried out, referred to above. While neither the PubMed search nor the extensive list of articles in Dr Siemiatycki's database can be considered complete, we used them to compile a list of journals in which such articles appeared. Putting these different elements together, we settled on 15 journals as the ones that were the main vehicles for publication of cancer case-control studies. Some of these journals did not exist for the entire period. There certainly may have been relevant studies in some other journals but these would have been few and we believed that the large investment of time of going through the journal issues one-by-one would not be justified by the number of pertinent articles we might find. Further, we restricted attention to articles published in certain mid-point calendar years in each decade. Further, because the issues in cancer studies may be distinct from those in some other disease studies, and so as to avoid mixing in too many issues, and because the numbers of studies that we could review was already very large with cancer studies, we restricted this investigation to cancer case-control studies. Further, because the issues of conducting such studies may be qualitatively different between advanced industrial societies and developing societies, both in terms of the systems available to ascertain and approach subjects, and the cultural framework in which people react to requests to participate in research, we tried to restrict attention to studies conducted in the main developed countries of North America and Europe and Australia or New Zealand. Further because the issues around soliciting participation

of children are different from those of soliciting participation among adults, and because there was already a very large number of studies to review among adults, we restricted attention to studies among adults.

No documentary record was maintained of this process. There was no attempt to identify and count all the journals that might conceivably report case-control studies. There was no attempt to identify and count all the articles that were published in those journals over the entire time period or during the selected years of publication. There was no attempt to count all the case-control studies that were conducted outside the selected countries. There was no attempt to identify and count all the case-control studies among children in those or other journals. There was no attempt to identify and count all the studies of diseases other than cancer in those or in other journals.

To summarize and to expand on the selection criteria, to provide a portrait of response rate reporting and response rate levels for the entire period of time without reviewing an inordinate number of publications, we instituted the following inclusion criteria: 1) Studies had to be published in one of the 15 selected journals during the following four sub-periods: 1984-1986, 1995, 2005, and 2013. We chose a 3-year period to represent the mid-1980s because of the relatively small number of studies per year before 1990. These journals and time periods defined the set of journal issues that we reviewed one-by-one to seek articles that satisfied the following criteria. 2) Studies had to focus on cancer etiology in adults. 3) Studies had to be conducted in North America, Europe, Australia, or New Zealand. 4) Studies had to have adopted the classic case-control design; nested case-control or case-cohort studies were excluded. 5) Studies had to include at least 50 cases or 50 controls, so as to minimize statistical instability of parameters of interest. 6) Studies had to entail data collection from subjects or their proxy respondents using

questionnaire instruments; pure record linkage studies were excluded. 7) We only included the latest publication if multiple reports were produced using the same case and control series.

If the selected publication did not mention subject participation, we sought relevant information from other reports by the study team. Two reviewers (MX and SC) independently screened every article in every issue of each journal in the targeted years, using the above criteria for inclusion. There was virtually perfect concordance between the reviewers. This was a qualitative informal comparison. In the rare case of uncertainty, the two reviewers consulted each other or other members of the team to achieve consensus decision on eligibility. No record was kept of instances of uncertainty. Figure 1 shows the flowchart of study sample selection.

4.2 Data Collection

For each eligible article, MX extracted the following detailed information: journal name, publication year, data collection period, location of the studied population, cancer type, type of control series (population, medical-source, and friends and/or family control series), mode of data collection (in-person, mail, telephone, or multiple methods), type of respondent accepted (self only, proxy only, or self and proxy), and terminologies used by authors to describe level of subject participation ("response rate", "participation rate", "cooperation rate", or multiple terminologies used). For each case and control series, we extracted information on eligible subjects, participants, subject refusal, subject deceased or too ill during the survey period if no proxy respondents were allowed or found, subject unreachable, and lastly subject not interviewed due to medical source obstacles (such as physicians refusing access to their subjects or medical staff being unable to carry out a gatekeeper function). When present, we also recorded each

study's eligibility criterion in regard to the presence of medical source obstacles for certain cases or controls.

It is not meaningful to try to distinguish between cases coming from population-based and from hospital-based studies because, unlike the controls in such studies, there is no necessary difference in the way such subjects are approached or their likely "state-of-mind". Further, the distinction between population-based and hospital-based studies is in fact often ambiguous. For instance, a study which ascertains cases from all hospitals and diagnostic centers in an area may be considered hospital-based by some, but in fact provides a complete "population-based" listing of cases. If the controls in such a study are selected from the general population via RDD or electoral lists or another such source, we would call them population-based controls. If the controls are selected from among patients with other diseases in the same hospitals in which the cases are ascertained, we would call them hospital-based controls. There is no rational basis for labelling cases as hospital-based or population-based on the basis of how the controls are selected. Nor is there any reason for thinking that cases would react differently if they are part of a study in which only the cases from one hospital are recruited versus a study in which cases from all hospitals in an area are recruited.

4.3 Response Rate definition

The response rate is defined as the number of participants divided by the number of eligible subjects. While the number of participants is easily defined, the number of eligible subjects, the denominator, can have different interpretations, depending on the investigators' treatment of different subsets of non-participants. The reasons for non-participation are typically: subject refusal, subjects deceased or too ill, subject unreachable for some reason, subject unable

to speak the local language, subject not contacted due to medical source obstacles (e.g. this might refer to a physician refusing access to a patient, or a member of medical staff failing to contact the patient). In a case-control study we endeavour to obtain data from a representative sample of cases in the study base and a representative sample of non-cases in the study base, conditional on certain covariates (13). Exclusion of any of the subsets of non-participants, whether among cases or controls, could lead to biased estimates of risk, and they will if the prevalence of exposure to the risk factor of interest differs by subset. Thus, in the absence of knowledge of exposure prevalence among all those subsets, one should endeavour to include them all, and failure to do so represents a threat to validity of the study's findings. Thus, the denominator for computing response rate should include all of the subsets of non-respondents listed above. The one exception to this rule is that if the study base can be legitimately redefined to exclude subjects in any of the subsets, and if that subset can be completely excluded from the study, then that subset does not need to be included in the denominator (or numerator) of response rate. Among the subsets listed above, the only one that could legitimately satisfy such criteria is the language problem subset. Consequently in assessing quality of reporting, we adopt the following definition of a response rate:

$$ResponseRate = \frac{Total\ Particpants}{Eligible\ Subjects}$$

$$Eligible\ Subjects = Total\ Particpants + Subject\ Refusal + Subject\ Deceased\ or\ Too\ Ill + Subject\ Unreachable + Medical\ Source\ Obstacle(if\ applicable)$$

4.4 Response Rate Reporting Quality Measurement

We examined the time trends of response rate reporting for the case, medical source control and population control series separately in our surveyed studies. In order for a reader to fully understand what the reported response rate in a paper truly means, it is necessary to know how the authors dealt with each of the components of "eligible subjects" in the above formula.

We created a scoring system to evaluate the quality of reporting of subject response rate; we assigned to each of these five components a reporting quality rating of either *"low", "medium",* or *"high"*. This rating was defined as: "low" = no information was provided in the study on this component and it cannot be calculated from information provided; "medium" = some information was provided, either explicitly or implicitly, that permitted an estimate of this component, but there was some ambiguity in the information that detracted from certainty (e.g., a response rate was provided but the number of eligible subjects was unknown); "high" = there was clear explicit information that allowed for an estimation of this component with high confidence (e.g., the number of eligible subjects and the response rate or the total number of participants were both explicitly provided).

In addition to assigning a quality rating for each component of response rate calculation of a study, we created an overall quality score to represent each study's overall response rate reporting quality. This score represents a study's overall presentation of number of true eligible subjects, number of true participants and true response rate. It is an ordinal score ranging from "0" to "3"; Score "0" indicates that no information was provided on subject participation; "1" indicates that there were information provided on eligible subjects and total participants, but no information was provided on reasons for non-participation; "2" indicates that there was information provided on eligible subjects, total participants, and some information on reasons for non-participation; and "3" indicates that there was comprehensive information provided on subject participation, including information on eligible subjects, total participants, and all 4 possible reasons for non-participation: subject refusal, subject deceased or too ill, subject unreachable, and medical source obstacle (when appropriate).

4.5 Response Rate Calculation

To the extent that the published papers provided the required data, we calculated response rates for each case and control series based on our formula presented above, and thus, the recorded response rates are not necessarily the same as the ones published by the investigators. When applicable, we also recorded whether studies treated non-respondents due to "medical source obstacles" as eligible. When studies did not provide sufficient information that allowed for a calculation of their response rates using the above formula, we recorded the rates reported by the authors.

4.6 Statistical analyses

We examined the time trends of response rates, separately for cases and each type of controls, using univariate linear regression models. Response rate (the outcome variable) was measured as the proportion of persons who participated, and time (the predictor variable) was measured as the mid-point year of data collection of each study, and was categorized into 4 time periods (1971-1980, 1981-1990, 1991-2000, 2001-2010); the period 1971-1980 was defined as the reference group. Time trends of each nonresponse rate (subject refusal, deceased or too ill, unreachable, and medical source obstacle(s)) were also examined using similar methodology. We also conducted sensitivity analyses using only self-respondent response rates, since the quality of interview conducted with proxies might be less reliable compared to that of self-respondents, which may result in information bias. To explore the yearly change in response rates within each time period and subject series, we carried out regression analyses using a linear spline model. Potential study design determinants of response rate for each subject series were examined using the following multivariate linear regression model: response rate (%) = b0 + b1x

cancer type (only applicable to cases) + b2 x study population (dichotomous) + b3 x mode of data collection (dichotomous) + b4 x type of respondent accepted + b5 x biologic sample collection + b6 x data collection period. All these potential determinants were considered to be the main independent variables and were entered together into the multivariate model; they were adjusted for each other and for time. The constant b0 represents the response rate for studies with the reference category for each variable. The other beta coefficients represent the percentage change in response rate for studies in the selected category when compared to the reference category, adjusted for the remaining variables. Potential study design determinants of response rate included study population (North America / Northern Europe, or others), cancer type (only applicable for cases), mode of data collection (in-person, or others), type of respondent accepted (self only, proxy only, or self and proxy), and biologic sample collection (invasive, non-invasive, or none). We also describe the response rates as a function of the quality of reporting of response rates. The reporting quality index for each study was derived by a method described by Xu et al (2016) (47); it ranges from 0 (no information) to 3 (full information).Tests of statistical significance were two sided, with an alpha level of 0.05. Statistical analyses were conducted using SPSS (IBM SPSS Statistics, Version 20.0. Armonk, NY: IBM Corp).

5 Manuscripts

The methodology and results of this investigation will be presented in two separate manuscripts. The first manuscript aims to describe the quality of reporting of response rates in case-control studies of cancer and the evolution of this reporting over time; the second manuscript aims to assess the current level and time trend of response rates in case-control studies of cancer, and to examine study design determinants that are associated with this rate.

5.1 Manuscript 1

Patterns and Trends in Quality of Reporting of Response Rates in Case-Control Studies of Cancer

Mengting Xu, Lesley Richardson, Sally Campbell, Javier Pintos, Jack Siemiatycki

Abstract

Background: The validity of results from case-control studies depends in part on response rates; however, inconsistent quality of reporting between studies hampers our ability to appreciate the true magnitude of response rates and the trend over time.

Objective: To describe the quality of reporting of response rates in published case-control studies of cancer over the past 30 years.

Methods: A review of case-control studies of cancer published in 15 major epidemiology, public health and general medicine journals was conducted. Four publication periods (1984-86, 1995, 2005 and 2013) were reviewed. Information on study base ascertainment, data collection methods, population characteristics, response rates, and reasons for non-participation was extracted. Quality of response rate reporting was assessed based on the amount of information reported.

Results: 370 studies conducted during 1961-2010 were reviewed, yielding a total of 370 case series and 422 control series. Overall, the quality of reporting of response rates and reasons for non-participation was poor. There was a tendency for better quality of reporting in case series, followed by population control series, and lastly by medical source control series. A peak in response rate reporting quality was observed in studies published in 1995. Reporting quality has deteriorated since then.

Conclusion: The reporting of relevant information on response rates in case-control studies of cancer was rather poor, which compromises our ability to assess validity of studies' findings. It would be helpful for a consensus to emerge regarding the reporting and calculation of response rate, based on the principle of maximal disclosure.

Key words: case-control studies; cancer; epidemiologic methods; response rate; participation rate

Background

In case-control studies, the response rate is often used as an indicator of the representativeness of a sample to the target population, and thus as an indicator of potential selection bias due to non-participation (14-17, 19, 30). It is widely believed that subject response rates in case-control studies of cancer have declined over the last decades (14, 48, 49), that the rate of this decline has increased in recent years, and that the decline was steeper in controls than in cases (16, 33). It is further believed that the declining response rate is a particular problem in case-control studies of cancer (32).

The term "response rate" is defined in different ways, and is often used interchangeably with other terms such as "participation rate" and "cooperation rate" (14). As defined in authoritative works of survey research (50) , participation rate is a general term and both "response rate" and "cooperation rate" are particular types of participation rate. Namely, "response rate" is defined as the number of complete interviews divided by the number of all potential eligible interviews, whereas "cooperation rate" is defined as the proportion of subjects interviewed divided by the number of eligible subjects ever contacted. The nuance between the two terms is that "response rate" includes the subjects that were unable to be contacted into the denominator but "cooperation rate" does not; hence by its nature, the "response rate" is a more conservative measure of the "participation rate" (14). Similarly, in epidemiologic usage, "response rate" is defined as the number of people interviewed divided by those who were eligible for the study (15, 20). Unfortunately, to date there is no universal standard for defining subject eligibility (the denominator) (19). For example, subjects who are unable to be contacted, are in poor health, are forbidden to be contacted by their physicians, or who do not speak the local

language, and hence are generally not interviewed are treated inconsistently by authors in terms of whether they should or should not be included in the denominator of response rate calculation (19, 20). Moreover, authors would often not report such information, leaving it impossible for readers to have a full disclosure of their eligibility criteria (50, 51).

Given that response rate is often used to indicate the potential for selection bias due to subject nonparticipation (14, 17, 26), it would make little sense to compare this rate between studies if it is defined, calculated, or reported differently in each study (14, 15, 17, 18). The lack of information provided would not only increase the opportunity for readers to misinterpret the validity of the reported risk estimates, but would also make it almost impossible to compare the potential of selection bias between studies (19, 20, 49, 52). Therefore, it is important that investigators report meaningful information about their computation of response rates. Unfortunately, the quality of reporting for this parameter is often questionable (14-16, 31, 53); moreover, it has been speculated that the quality of reporting has deteriorated over time (20). The aim of our study was to describe the quality of reporting of response rates in case-control studies of cancer and the evolution of reporting quality over the past 30 years.

Methods

Sample selection of published studies

This is a review of questionnaire-based case-control studies of cancer that were published over the past 30 years. In a preliminary exercise we established that PubMed and other automatic search methods were not reliable in identifying all case-control studies, and even less, in identifying those that reported response rates. We realized that

we would have to review all articles in certain journals one-by-one. Given the enormous number of studies in all journals and the practical limitation of being able to review them all, we instituted a strategy to restrict numbers but yet maintain relevance. Based on our large bank of reprints of cancer case-control studies published since the 1980s, we identified fifteen international journals of epidemiology, public health and general medicine that seemed to be the main vehicles for publication of epidemiological studies of cancer during this period. Some of the selected journals did not exist for the entire period. We further restricted attention to articles published in certain calendar years in each decade, namely 1984-1986, 1995, 2005, and 2013. For those selected journals and those years, we "manually" examined each issue and each article, and selected those that satisfied the following additional inclusion criteria: 1) We restricted attention to case-control studies focusing on etiology of cancer in adults. 2) Fifteen major journals of epidemiology, public health and general medicine that we believed to be the main vehicles for publication of epidemiological studies of cancer during the past 30 years, were selected. Some of these journals did not exist for the entire period. 3) Four sub-periods of publication were selected: 1984-1986, 1995, 2005, and 2013. We chose a 3-year period to represent the mid-1980s because the number of studies per year was much lower before 1990. 4) The studies were conducted in North America, Europe, Australia, or New Zealand. 5) The studies involved the classic case-control design; nested case-control or case-cohort studies were excluded. 6) There were at least 50 cases or 50 controls in the studies, so as to minimize statistical instability of parameters of interest. 7) The study entailed data collection from subjects or their proxy respondents using questionnaire instruments; pure record linkage studies were excluded. 8) If multiple

publications were produced based on the same case and control series, we only included the latest publication. If a selected study referred to a previous publication for more detailed information on study methods, we extracted information on subject participation from its previous publication. Two reviewers (MX and SC) independently screened every article in every issue of each journal in the targeted years, using the above criteria for inclusion. There was a virtually perfect concordance between the reviewers. This was a qualitative informal comparison. In the rare case of uncertainty, the two reviewers consulted each other or selected members of the team to achieve consensus decision on eligibility. Figure 1 shows the flowchart of study selection.

Data Collection

For each eligible article, we collected information on contextual characteristics of publications, such as journal name and publication year. We also collected information on study design and study population characteristics, including cancer type examined (categorized based on cancer cell morphology and patient survival rate), location of the studied population, study's data collection period, and types of control series, the main types being population controls and medical source controls, and friends and/or family controls. Population control series could be selected from sources such as population registers, electoral lists, random digit dialing, driver's license, governmental medical insurance lists and neighbours of cases. The medical source control series were selected from sources such as hospitals, Health Maintenance Organization (HMO) or General Practitioner (GP) lists, and cancer or death registers. Data collection methods of the surveyed studies were recorded into the following variables: mode of data collection (in-person, mail, telephone, or multiple methods), type of respondent accepted (self-only,

proxy-only, or self and proxy), use of financial incentives (Y/N), persons responsible for soliciting subject participation (research team or medical personnel).We also recorded the terminology used by authors to describe "response rate" ("response rate", "participation rate", "cooperation rate", or multiple terminologies used).

For each study, we extracted separately for case and each control series the information on eligible subjects, participants, subject refusal, subject deceased or too ill during the survey period and no proxy respondents were allowed or found, subject unreachable, and lastly subject not interviewed due to medical source obstacle (such as physicians refusing access to their subjects or medical staffs being unable to carry out a gatekeeper function). When present, we also recorded each study's eligibility criterion in regard to the presence of medical source obstacles for certain cases or controls.

Response Rate definition

The response rate was defined as the number of participants divided by the number of eligible subjects. While the number of participants is easily defined, the number of eligible subjects, the denominator, can have different interpretations, depending on the investigators' treatment of different subsets of non-participants. The reasons for non-participation are typically: subject refusal, subjects deceased or too ill, subject unreachable for some reason, subject unable to speak the local language, subject not contacted due to medical source obstacles (e.g. this might refer to a physician refusing access to a patient, or a member of medical staff failing to contact the patient). In a case-control study we endeavour to obtain data from a representative sample of cases in the study base and a representative sample of non-cases in the study base, conditional on certain covariates (54). Exclusion of any of the subsets of non-participants, whether

among cases or controls, could lead to biased estimates of risk, and they will if the prevalence of exposure to the risk factor of interest differs by subset. Thus, in the absence of knowledge of exposure prevalence among all those subsets, one should endeavour to include them all, and failure to do so represents a threat to validity of the study's findings. Thus, the denominator for computing response rate should include all of the subsets of non-respondents listed above. The one exception to this rule is that if the study base can be legitimately redefined to exclude subjects in any of the subsets, and if that subset can be completely excluded from the study, then that subset does not need to be included in the denominator (or numerator) of response rate. Among the subsets listed above, the only one that could legitimately satisfy such criteria is the language problem subset. Consequently in assessing quality of reporting, we adopt the following definition of a response rate:

$$ResponseRate = \frac{Total\ Particpants}{Eligible\ Subjects}$$

$$Eligible\ Subjects = Total\ Particpants + Subject\ Refusal + Subject\ Deceased\ or\ Too\ Ill + Subject\ Unreachable + Medical\ Source\ Obstacle(if\ applicable)$$

Response Rate Reporting Quality Measurement

We examined the time trends of response rate reporting for the case, medical source control and population control series separately in our surveyed studies. In order for a reader to fully understand what the reported response rate in a paper truly means, it is necessary to know how the authors dealt with each of the components of "eligible subjects" in the above formula. We created a scoring system to evaluate the quality of reporting of subject response rate; we assigned to each of these five components a reporting quality rating of either *"low", "medium",* or *"high"*. This rating was defined as: "low" = no information was provided in the study on this component and it cannot be calculated from information provided; "medium" = some information was provided,

either explicitly or implicitly, that permitted an estimate of this component, but there was some ambiguity in the information that detracted from certainty (e.g., a response rate was provided but the number of eligible subjects was unknown); "high" = there was clear explicit information that allowed for an estimation of this component with high confidence (e.g., the number of eligible subjects and the response rate or the total number of participants were both explicitly provided).

In addition to assigning a quality rating for each component of response rate calculation of a study, we created an overall quality score to represent each study's overall response rate reporting quality. This score represents a study's overall presentation of number of true eligible subjects, number of true participants and true response rate. It is an ordinal score ranging from "0" to "3"; Score "0" indicates that no information was provided on subject participation; "1" indicates that there were information provided on eligible subjects and total participants, but no information was provided on reasons for non-participation; "2" indicates that there was information provided on eligible subjects, total participants, and some information on reasons for non-participation; and "3" indicates that there was comprehensive information provided on subject participation, including information on eligible subjects, total participants, and all 4 possible reasons for non-participation: subject refusal, subject deceased or too ill, subject unreachable, and medical source obstacle (when appropriate).

Results

This review included 370 case-control studies of cancer (Figure 1). We excluded three journals due to a lack of published studies meeting our inclusion criteria. As shown in Table 1, one general epidemiology and three cancer journals accounted for nearly 80%

of the studies meeting the inclusion criteria. There were approximately equal numbers of studies selected in the years representing each decade of publication, except for a bulge in 2005. The most studied cancer types were breast, cervix or endometrial cancers (22%), lung, mesothelioma or respiratory tract cancers (11%), and hematopoietic cancers (10%). Two-thirds of studies were conducted in North American populations with the rest spread in the other eligible regions. The median year of data collection ranged from 1961 to 2010, with a large majority (37%) of studies occurring between 1991-2000. 51 of the 370 studies used multiple control series in their studies, yielding a total of 370 case series and 422 control series in our data. Of these control series, 66% were selected from the general population, 31% were selected from medical sources (hospitals, clinics, HMO or GP lists, and cancer or death registers) and 3% were selected from friends and/or family of cases. Because such a small number of studies used friend or family controls, we did not include these in our analyses. As for mode of data collection, 69% of studies collected data from subjects in person, 10% through mail, 8% through telephone, and 12% through multiple methods. 80% of studies only interviewed subject respondents; nearly all the rest accepted proxy response.

Whether or not financial incentives were used to encourage subject participation was rarely reported (<3%). The same was true regarding the reporting of persons responsible for soliciting subjects' participation (6%). Among the 364 applicable case series, only 30% reported their eligibility criterion on non-participants due to medical source obstacles, and among those, 79% considered those non-participants as eligible for purposes of computing response rates. Among the 126 applicable medical source series, only 10% reported their eligibility criterion on non-participants due to medical source

obstacles, and among those, 58% considered those non-participants as eligible for purposes of computing response rates.

Quality of reporting of response rates

The overall quality score of response rate reporting in the case, medical source control, and population control series are presented by publication year in Table 2.

The case and population control series had a very similar pattern for overall quality of response rate reporting. 16% and 13% of studies had an overall quality score of "0", for the reporting of the case and population control series, respectively. Of the remaining studies, in both series, the proportion of studies declined as the score increased. Only 12% and 11% of studies had an overall quality score of "3", for the reporting of the case and population control series, respectively. In addition, time trends for the reporting of these two series showed a decline in studies with a score of "0" and "2", an increase in studies with a score of "1", and a peak in 1995 publications in studies with a score of "3". The pattern of overall quality of response rate reporting for the medical source control series differed from that for the case and population control series. Nearly half of such studies had an overall quality score of "0". Few of the reports of the medical source control series had scores greater than or equal to "2". Moreover, despite some fluctuations, the pattern of response rate reporting for the medical source control series did not seem to have changed over time.

Further, we subdivided the case series into those from studies in which population controls were exclusively used and those from studies in which medical source controls were exclusively used. Interestingly, the quality of the reporting regarding cases was

better when the study used population controls than when medical source controls were used (see Appendix Table A).

The reporting of response rates and each component of reasons for non-participation for the case, medical source control and population control series is presented in Table 3. Overall, reporting quality for both response rates and reasons for non-participation were the highest in cases, followed by population controls, and lastly by medical source controls. 60%, 52% and 31% of studies had a "high" quality rating for the reporting of response rates, for the case, population control and medical source control series, respectively. For the reporting of reasons for non-participation, each component was more often reported for the case series than for the population and medical source control series. Subject refusal was the most reported reason for non-participation in all three series.

As we did in relation to overall quality, we compared the components of quality between cases from studies that used exclusively population controls with those that used exclusively medical source controls. As shown in Appendix Table B, the reporting of response rate and other components were worse for cases in medical-source-based than in population-based studies.

Discussion

There was rather poor reporting of relevant information on subject response rates in case-control studies of cancer, especially regarding reasons for non-participation. In addition, subject eligibility criteria were often unclear. Although the proportion of studies not reporting any information on response rates has declined slightly over time, overall

reporting quality did not seem to have improved substantially. There was a tendency for better quality of reporting in case series, followed by population control series, and lastly by medical source control series. Further, the authors of studies using population controls were more assiduous in their reporting practices than authors of studies using medical source controls. This latter phenomenon may be partly explained by two factors. There were proportionately more population-based controls used in more recent years, and perhaps this just reflects a temporal trend in quality of reporting. A second conjecture is that there has been a tendency for investigators with clinical research credentials to be more likely than investigators with epidemiology credentials to have undertaken proportionately more studies using medical source controls.

It seems that many authors did not have a clear understanding of the distinction between "response rate", "participation rate", and "cooperation rate", as the terms were often used interchangeably. This problem is particularly apparent in studies for which full subject eligibility could not be ascertained at the initial stage, such as in studies using random digit dialing. For example, some studies would calculate the overall response rate by multiplying the screening response rate and the interview response rate while other studies would simply refer to the interview response rate as the overall response rate (17). While it is reasonable to exclude ineligible subjects from the denominator of response rate; it is, however, difficult to define correctly and consistently "eligibility". For example, Harris (19) pointed out in her commentary that some studies tended to exclude deceased and unreachable subjects from the denominator of response rate while other studies did not. The consequence of having different definitions of eligibility in common usage can be detrimental. As Nattinger et al. (44) demonstrated, changing the definition

of "eligible subject" could modify their subject response rate from 57% to 70%. In the context of case-control studies of cancer where the sampling frame usually differs between case and control series, poorly or incorrectly defined eligibility criteria for cases and controls could cause an unpredictable level of selection bias and threatens a study's generalizability, despite a reported high response rate.

We observed different levels of reporting for subject eligibility due to medical source obstacles between case and medical source control series. Despite a general lack of reporting, more studies reported this eligibility criterion for cases than for medical source controls. Reports about case series were more likely to acknowledge and properly report obstacles in subject ascertainment due to medical personnel than were reports about medical source controls (79% and 58% of studies, respectively). Authors may be more assiduous in reporting about cases than controls. This may be a growing problem as the requirements of ethical review bodies increasingly restrict access of researchers to human subjects without some type of intercession by medical personnel (14, 20, 25, 44). Since medical personnel are already overworked, it is problematic to have to rely on them to recruit subjects for epidemiologic research. The nature and quality of such intervention is not easily controllable by the researchers, and this leads to losses of potential subjects, and perhaps to losses of unrepresentative samples of subjects (42, 43). We do not consider subjects not interviewed due to language reasons an essential component of response rate, since the study base can legitimately be defined as members of the population who speak the local language, without compromising internal validity; however such exclusion has to be performed equivalently for cases and controls.

Although the current reporting of response rates in case-control studies of cancer is better than that in the 1980s, the proportion of 2013 studies reporting their response rates was still relatively low, and it was much lower than what was observed in 1995. Some commentators (16, 20, 55) have opined that the lack of reporting of response rates and of the methods used to calculate it is due to the popular perception that studies with low response rates are inferior to studies with higher rates. Consequently, authors would feel pressure to avoid presenting explicit information that could decrease their chance of being published. For example, one study (55) surveyed the chief editors from 18 journals and found out that none of the journals had a formal policy for the reporting of study participation or a required minimal response rate for publication, although one editor asserted that studies with response rates below 60% were rarely published in their journal. Another potential factor in the self-censoring of information regarding response rates is word count limit for many journals, especially the relatively high impact journals. In the fierce competition for space in a manuscript, the authors may well sacrifice the apparently dry and potentially harmful information about their response rates for information about the study's substantive findings, an unfortunate trade-off. However, some journals have acknowledged this issue and are trying to resolve it. For example, one journal editor (56) encouraged authors to use online supplementary appendices to provide full disclosures of subject response rates and reasons for non-participation.

Previous studies reported that 56% (16) of case-control studies and 47% (50) of all epidemiologic studies provided no information regarding their response rates. In our sample, the proportions of studies providing no information were lower. This could be due to the fact that we also reviewed and extracted information on study participation

from previous methodological publications of our surveyed studies. Our findings were in line with another study that examined the reporting of response rate in 117 survey studies published from 34 medical journals (51). Similar to us, they reported that 76% of their surveyed studies provided at least some information on subject response rates, but a majority of them (87%) did not report clearly how the rate was calculated and did not provide reasons for non-participation. In addition, in keeping with Morton et al.'s finding (16), we also observed that population-based case-control studies tended to report more often information on response rates than did medical-source-based studies. Our findings on the overall quality of response rate reporting showed that, over time, although fewer studies reported no information on this parameter, most studies still only reported minimal information on response rates. Moreover, we observed that the quality of reporting seemed to peak in our 1995 sample. We hypothesize that it improved up to that point because of increasing awareness of the importance of response rate as a contributor to study quality, and it declined afterwards because of the reasons alluded to above, namely, the increase in subject refusal and the increasing difficulties in accessing subjects due to ethical constraints leading to declining response rates, resulting in a greater reluctance to reveal the true response rates to journal editors and reviewers, coupled with increasing pressure on word counts. Nor did we observe much in the way of elucidation of methods used to enhance participation, such as the role or title of the person in charge of soliciting subject participation and the use of financial incentives, both of which may influence subject's response rate (14, 15, 18, 27). While such information is not essential to deriving a true response rate, it nevertheless would be useful to understand reasons for

particularly high or low response rates and could inform researchers contemplating new studies.

There are a few considerations that may affect the interpretation of our study. First, as there is no consensus in how response rate should be calculated and reported, others may find that our definition, which includes the major sources of nonresponse in the denominator, is too conservative or rigid. Second, we selected for this review 15 journals that in our view were likely to have published a large fraction of epidemiological case-control studies of cancer. There have been other journals, but in our view these would not have accounted for large numbers of articles of the types we were searching for, and in any case, the journals we selected probably represent the "best case scenarios" of high quality epidemiology journals. Articles published elsewhere may well have been of lower quality on average. Our focus on case-control studies of cancer, rather than on a broader tableau of possible designs and content areas has both pros and cons. Although it does not provide an overview of the reporting of response rates in epidemiologic studies, we were able to explore the practice of response rate reporting in this paradigm in depth and ensure that our findings over time are not confounded by shifting proportions of study designs or disease outcomes. In addition, our large sample size comprised of studies published in the past three decades enabled us to explore in detail the current and past practice of reporting of response rates and reasons for non-participation.

Conclusion

Response rates have not been well or consistently reported, in case-control studies of cancer. Given the perceived decline of subject participation in case-control studies of cancer, the lack of transparency in reporting and consistency in calculating response rate

make it difficult to properly take stock of the situation. Although efforts have been made to improve the overall reporting quality of observational epidemiologic studies through, for example, the publication of *Strengthening the Reporting of Observation Studies in Epidemiology (STROBE)* statement (31, 57), the impact of such initiatives is yet to be manifested. It would be helpful for a consensus to emerge regarding the reporting and calculation of response rate, based on the principle of maximal disclosure.

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Tables and Figure

Table 1. Frequency distributions of the surveyed studies

	No.	%
All	**370**	
Journal		
CEBP	83	22.4
AJE	71	19.2
CCC	68	18.4
IJC	63	17.0
Others[1]	85	23.0
Publication year		
1984-1986	75	20.3
1995	83	22.4
2005	140	37.8
2013	72	19.5
Cancer type		
Breast, cervix, endometrium	83	22.4
Lung, mesothelioma, respiratory tract	42	11.4
Hematopoietic	36	9.7
Prostate, testicle, penis	32	8.6
Head and neck	30	8.1
Colorectum	28	7.6
Bladder, kidney, urinary tract	27	7.3
Ovary	23	6.2
Stomach, liver, pancreas	22	5.9
Skin	16	4.3
Brain	15	4.1
Others	16	4.3
Study population		
North America (USA and Canada)	245	66.2
Southern Europe[2]	51	13.8
Northern Europe[3]	41	11.1
Eastern Europe[4]	8	2.2
Australia or New Zealand	16	4.3
Multiple	9	2.4
Median year of data collection		
1961-1980	63	17.0
1981-1990	103	27.8
1991-2000	138	37.3
2001-2010	59	15.9
Not mentioned	7	1.9
Type of control series[5]		
Population [6]	278	65.9
Medical source[7]	131	31.0
Friends and family	13	3.1
Mode of data collection		
In-person	256	69.2
Mail	36	9.7
Telephone	31	8.4
Multiple methods	43	11.6
Not mentioned	4	1.1
Type of respondent accepted		
Self only	297	80.3
Proxy only	6	1.6
Self and proxy	64	17.3
Not mentioned	3	0.8
Use of Financial incentives		
Yes	8	2.2
No	1	0.3
Not mentioned	361	97.6
Persons soliciting participation		
Research team	14	3.8
Medical personnel	7	1.9
Not mentioned	349	94.3

1. All other journals listed in Figure 1, except for Prostate, Lung Cancer and Journal of Epidemiology and Community Health, which had no studies meeting the inclusion criteria.

2. Southern Europe: Spain, Portugal, Italy, Greece, France.

3. Northern Europe: Finland, Sweden, Norway, Denmark, Netherlands, including Germany and United Kingdom.

4. Eastern Europe: Russia, Poland, Czech Republic, Slovakia, Hungary, Romania, Bulgaria, Turkey, Slovenia.

5. The sum of the percentage of each type of control series do not add up to 100 because some studies used more than one type of control series.

6. Includes sources such as population registers, electoral lists, random digit dialing, driver's license, governmental medical insurance lists and neighbors of cases.

7. Includes such sources as hospital or clinic patients, HMO or GP lists, and cancer or death registers.

Table 2. Overall quality of response rate reporting in surveyed studies by publication year, and by type of subject series (case series, medical source control series, population control series)

Overall score (Range: 0-3*)		Publication year									
		1984-1986		1995		2005		2013		Overall	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
Cases	0	18	(24.0)	13	(15.7)	17	(12.1)	10	(13.9)	58	(15.7)
	1	21	(28.0)	29	(34.9)	61	(43.6)	38	(52.8)	149	(40.3)
	2	33	(44.0)	26	(31.3)	44	(31.4)	16	(22.2)	119	(32.2)
	3	3	(4.0)	15	(18.1)	18	(12.9)	8	(11.1)	44	(11.9)
	Total	75	(100)	83	(100)	140	(100)	72	(100)	370	(100)
Medical Source Controls	0	19	(46.3)	12	(44.4)	22	(44.0)	7	(53.8)	60	(45.8)
	1	11	(26.8)	11	(40.7)	17	(34.0)	4	(30.8)	43	(32.8)
	2	10	(24.4)	4	(14.8)	11	(22.0)	2	(15.4)	27	(20.6)
	3	1	(2.4)	0	(0.0)	0	(0.0)	0	(0.0)	1	(0.8)
	Total	41	(100)	27	(100)	50	(100)	13	(100)	131	(100)
Population Controls	0	8	(21.1)	7	(10.8)	12	(11.4)	9	(12.9)	36	(12.9)
	1	15	(39.5)	32	(49.2)	65	(61.9)	43	(61.4)	155	(55.8)
	2	12	(31.6)	17	(26.2)	15	(14.3)	13	(18.6)	57	(20.5)
	3	3	(7.9)	9	(13.8)	13	(12.4)	5	(7.1)	30	(10.8)
	Total	38	(100)	65	(100)	105	(100)	70	(100)	278	(100)

* The overall score represents a study's overall presentation of number of true eligible subjects, number of true participants and true response rate.

The scores are assigned with an ordinal score from 0 to 3 (0 being the least informative).

0: No information on subject participation

1: Information provided on eligible subjects and participants, but no information on reasons for non-participation

2: Information provided on eligible subjects, participants, and some information on reasons for non-participation

3: Comprehensive information on subject participation (provide information on participants and all 4 reasons for non-participation including subject refusal, medical source obstacle, subject deceased or too ill, and subject unreachable, so the number of eligible subjects could be calculated as the sum of participants and non-participants if it was not given explicitly)

Table 3. Quality of reporting of information on components of response rates in surveyed studies, by type of subject series (case series, medical source control series, and population control series)

	Cases n=370 series			Medical source controls n=131 series			Population controls n=278 series		
	Quality[a]			Quality[a]			Quality[a]		
	Low[b]	Medium[b]	High[b]	Low	Medium	High	Low	Medium	High
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Information provided [c]									
Eligible subjects	148 (40.0)		222 (60.0)	88 (67.2)		43 (32.8)	132 (47.5)		146 (52.5)
Total participants	58 (15.7)	93 (25.1)	219 (59.2)	60 (45.8)	30 (22.9)	41 (31.3)	36 (12.9)	98 (35.3)	144 (51.8)
Non-participation reasons									
Subject refusal	239 (64.6)	24 (6.5)	107 (28.9)	102 (77.9)	15 (11.5)	14 (10.7)	200 (71.9)	12 (4.3)	66 (23.7)
Medical source obstacle[d]	279 (76.6)	8 (2.2)	77 (21.2)	127 (96.9)	1 (0.8)	3 (2.3)	-	-	-
Subject deceased or too ill[e]	262 (70.8)	12 (3.2)	96 (25.9)	123 (93.9)	0 (0.0)	8 (6.1)	237 (85.3)	3 (1.1)	38 (13.7)
Subject unreachable	279 (75.4)	7 (1.9)	84 (22.7)	122 (93.1)	0 (0.0)	9 (6.9)	218 (78.4)	7 (2.5)	53 (19.1)

a. The quality rating was based on a review of the paper by MX. The general algorithm was: Low = no information is provided in the paper on this component and it cannot be calculated from information provided; Medium = some information is provided, either explicitly or implicitly, that permits an estimate of this component, but there is some ambiguity in the information that detracts from certainly; High = there is clear explicit information that allows for an estimation of this component with high confidence.

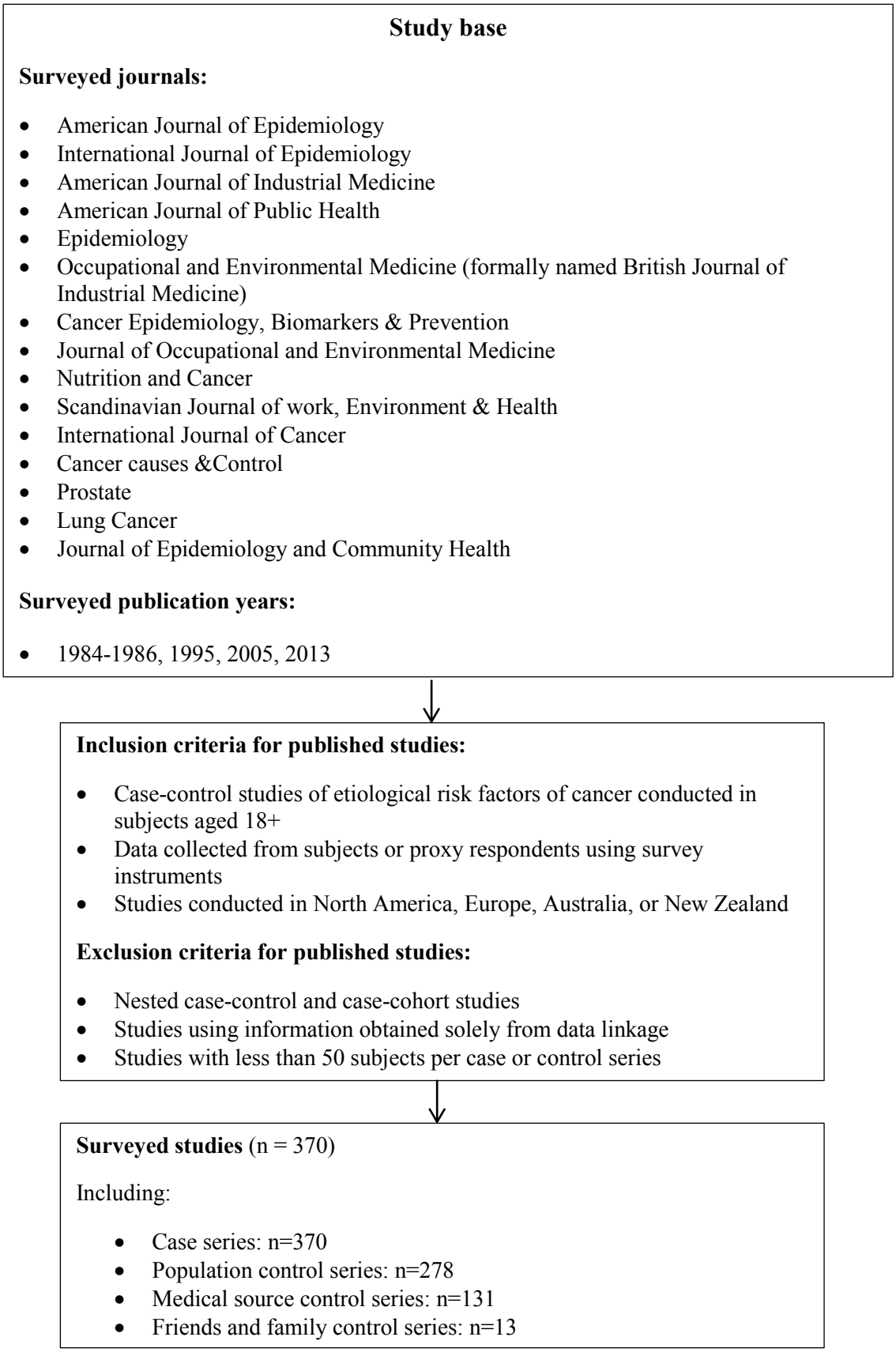
b. The values in this column represent the percentage of studies that fall into these quality categories.

c. The information needed to ascertain the response rate is the denominator (eligible subjects) and the numerator (participants). But this is not enough if the authors have not made it clear how they dealt with various reasons for non-participation. It should be evident to the reader how many subjects did not participate, by reasons for non-participation, and how these subjects were dealt with in defining the "eligible subjects".

d. This could include the patient's physician refusing access to the patient, or the medical staff being unable to carry out a gatekeeper function. 6 case series and 5 medical control series were excluded because only the proxies of deceased subjects were interviewed.

e. This could include the subject was deceased or too ill and no proxy was allowed or found.

Figure 1. Surveyed study selection method



Appendix Table A. Overall response rate reporting quality of the case series in surveyed studies by publication year presented separately for studies that used exclusively medical-source-based controls and population controls.

Case series											
Overall score (Range: 0-3*)		Publication year 1984-1986		1995		2005		2013		Overall	
		n	(%)	n	(%)	n	(%)	n	(%)	n	(%)
In studies using exclusively medical-source-based controls	0	13	(40.6)	10	(40.0)	11	(28.9)	5	(45.5)	39	(36.8)
	1	11	(34.4)	10	(40.0)	16	(42.1)	2	(18.2)	39	(36.8)
	2	8	(25.0)	5	(20.0)	11	(28.9)	4	(36.4)	28	(26.4)
	3	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)
	Total	32	(100)	25	(100)	38	(100)	11	(100)	106	(100)
In studies using exclusively population-based controls	0	2	(7.4)	1	(1.9)	3	(3.6)	4	(7.1)	10	(4.6)
	1	6	(22.2)	18	(34.0)	34	(41.0)	33	(58.9)	91	(41.6)
	2	16	(59.3)	20	(37.7)	29	(34.9)	12	(21.4)	77	(35.2)
	3	3	(11.1)	14	(26.4)	17	(20.5)	7	(12.5)	41	(18.7)
	Total	27	(100)	53	(100)	83	(100)	56	(100)	219	(100)

* The overall score represents a study's overall presentation of number of true eligible subjects, number of true participants and true response rate.

The scores are assigned with an ordinal score from 0 to 3 (0 being the least informative).

0: No information on subject participation

1: Information provided on eligible subjects and participants, but no information on reasons for non-participation

2: Information provided on eligible subjects, participants, and some information on reasons for non-participation

3: Comprehensive information on subject participation (provide information on participants and all 4 reasons for non-participation including subject refusal, medical source obstacle, subject deceased or too ill, and subject unreachable, so the number of eligible subjects could be calculated as the sum of participants and non-participants if it was not given explicitly)

Appendix Table B. Reporting quality of information on components of response rates of the case series in surveyed studies, presented separately for studies that used medical-source-based controls and population controls.

	Case series					
	In studies using exclusively medical-source-based controls n=106 series			In studies using exclusively population-based controls n=219 series		
	Quality[a]			Quality[a]		
	Low[b]	Medium[b]	High[b]	Low	Medium	High
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Information provided [c]						
Eligible subjects	69 (65.1)		37 (34.9)	57 (26.0)		162 (74.0)
Total participants	39 (36.8)	31 (29.2)	36 (34.0)	10 (4.6)	48 (21.9)	161 (73.5)
Non-participation reasons						
Subject refusal	80 (75.5)	14 (13.2)	12 (11.3)	130 (59.4)	8 (3.7)	81 (37.0)
Medical source obstacle[d]	97 (97.0)	1 (1.0)	2 (2.0)	-	-	-
Subject deceased or too ill[e]	101 (95.3)	1 (0.9)	4 (3.8)	129 (58.9)	10 (4.6)	80 (36.5)
Subject unreachable	102 (96.2)	0 (0.0)	4 (3.8)	146 (66.7)	7 (3.2)	66 (30.1)

a. The quality rating was based on a review of the paper by MX. The general algorithm was: Low = no information is provided in the paper on this component and it cannot be calculated from information provided; Medium = some information is provided, either explicitly or implicitly, that permits an estimate of this component, but there is some ambiguity in the information that detracts from certainly; High = there is clear explicit information that allows for an estimation of this component with high confidence.

b. The values in this column represent the percentage of studies that fall into these quality categories.

c. The information needed to ascertain the response rate is the denominator (eligible subjects) and the numerator (participants). But this is not enough if the authors have not made it clear how they dealt with various reasons for non-participation. It should be evident to the reader how many subjects did not participate, by reasons for non-participation, and how these subjects were dealt with in defining the "eligible subjects".

d. This could include the patient's physician refusing access to the patient, or the medical staff being unable to carry out a gatekeeper function. This component only applies to 364 studies in the case series because in 6 studies only the proxies of deceased subjects were interviewed.

e. This could include the subject was deceased or too ill and no proxy was allowed or found.

5.2 Manuscript 2

Time Trends and Study Design Determinants of Response Rates in Case-Control Studies of Cancer

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Abstract

Low subject participation increases the potential of selection bias in case-controls studies, which in turn may weaken the validity of risk estimates. There is concern that response rate in epidemiologic studies has declined over the past decades. To assess this issue in case-control studies of cancer and to identify study design determinants of response rate, the authors conducted a review of data from 370 case-control studies of cancer published in 15 epidemiology, public health, or general medical journals during four periods: 1984-1986, 1995, 2005, and 2013. Univariate linear regression models were used to analyse time trends of response rate in studies conducted during 1971-2010. Multivariate linear regression models adjusted for time and other study design factors were used to examine study design determinants of response rate. Participation has declined over the past 30 years, and this decline was steeper in studies conducted after 2000. When compared to the response rates in the period of 1971-1980, there was a greater decline of this rate in population controls (-17.04%, 95% CI: -23.17%, -10.91%) than in cases (-5.99%, 95% CI: -11.50%, -0.48%). Statistically significant study design determinants for cases' participation were cancer type examined, location of study population, and mode of data collection. The only determinant for medical source controls' participation was location of study population, and the only determinant for population controls' participation was type of respondent accepted. The authors conclude that response rates in case-control studies of cancer seem to have declined and this decline has accelerated in recent studies, especially among population controls, which threatens the credibility of results derived from case-control studies of cancer.

Key words: case-control studies; cancer, epidemiologic methods; response rate; participation rate, data collection

Introduction

The case-control study design is the most practical and efficient design to examine the causal relationship of exposures to rare diseases with long induction period such as cancer, and it has contributed greatly in improving our understanding of the etiology of this disease (2, 58). To ensure the internal validity of a case-control study, we aim to enroll representative samples of cases and of controls from the same source population. The selected controls should provide an unbiased estimate of prevalence of exposure and covariates in the source population that gave rise to the cases (3, 59). Selection bias occurs when this principle is violated. One form of such bias is nonresponse bias, which arises when participation is differential by exposure and by disease status (3). Although case-control studies with low subject response rates do not necessarily produce biased risk estimates, they are more susceptible to nonresponse bias than studies with higher participation. It is widely believed that subject response rates in epidemiologic studies have declined over the last decades (14); however, the magnitude and reasons of this change, and whether it is present in all epidemiological study designs are still unclear. Previous time trend assessments of response rates in epidemiologic studies were impeded by insufficient reporting of subject participation and inconsistent methods for response rate calculation in published studies. Moreover, there has been little investigation of this phenomenon in the past decade.

We therefore conducted a review of studies published from 1984-2013 to assess the time trends of response rates in case-control studies of cancer and to examine study design factors that are associated with this rate.

Materials and methods

Sample selection

This is a review of questionnaire-based case-control studies of cancer that were published over the past 30 years. In a preliminary exercise we established that PubMed and other automatic search methods were not reliable in identifying all case-control studies, and even less, in identifying those that reported response rates. We realized that we would have to review all articles in certain journals one-by-one. Given the enormous number of studies in all journals and the practical limitation of being able to review them all, we instituted a strategy to restrict numbers but yet maintain relevance. Based on our large bank of reprints of cancer case-control studies published since the 1980s, we identified fifteen international journals of epidemiology, public health and general medicine that seemed to be the main vehicles for publication of epidemiological studies of cancer during this period. Some of the selected journals did not exist for the entire period. We further restricted attention to articles published in certain calendar years in each decade, namely 1984-1986, 1995, 2005, and 2013. For those selected journals and those years, we "manually" examined each issue and each article, and selected those that satisfied the following additional inclusion criteria: 1) Samples were restricted to case-control studies focusing on cancer etiology in adults. 2) Four sub-periods of publication were selected: 1984-1986, 1995, 2005, and 2013. A 3-year period was selected to represent the mid-1980s because of the small number of studies per year before 1990. 3) Studies had to be conducted in North America, Europe, Australia, or New Zealand. 4) Studies had to have adopted the classic case-control design; nested case-control or case-cohort studies were excluded. 5) Studies had to include at least 50 cases or 50 controls in the studies, so as to minimize statistical instability of parameters of interest. 6) Studies had to entail data collection from subjects or their proxy

respondents using questionnaire instruments; pure record linkage studies were excluded. 7) If multiple publications were produced based on the same case and control series, only the latest publication was included. If subject participation information was not mentioned in the selected publication, we sought relevant information from other reports by the study team. Figure 1 shows the flowchart of study sample selection.

Data collection

Two reviewers (MX and SC) independently screened every article in every issue of each journal in the targeted years, using the above criteria for inclusion. There was a virtually perfect concordance between the reviewers. This was a qualitative informal comparison. In the rare case of uncertainty, the two reviewers consulted each other or selected members of the team to achieve consensus decision on eligibility. For all eligible studies, we extracted journal name; publication year; data collection period; location of the studied population; examined cancer type (categorized based on cancer cell morphology and patient survival rate); types of control series (population, medical-source, and friends and family control series); mode of data collection (in-person, mail, telephone, or multiple methods); types of respondent accepted (self only, proxy only, or self and proxy); and biologic sample collection (Invasive methods, non-invasive methods, none). For each reported case and control series, we extracted information on response rates and reasons for non-participation.

Response rate calculation

The response rate of a study is calculated as the number of participants divided by the number of eligible subjects (20). Although theoretically straightforward, there is no standardized definition of what constitutes an "eligible" subject in epidemiologic studies (19). In a case-control design, we aim to obtain subjects from a representative sample of the source population,

and the controls should be from the same study base as the cases, conditional on certain covariates (59). Exclusion of non-respondents for any reason, whether among cases or controls, could lead to biased risk estimates if participation differs by exposure and by disease status. The reasons that may cause non-participation in a case-control study are: subject refusal, subject deceased or too ill, subject unreachable, subject unable to speak the local language and when appropriate, subject not contacted due to medical source obstacle(s). (This refers to physicians refusing access to their patients, or that members of medical staffs failing to contact the patients.) Each of these reasons could conceivably be correlated with the exposure factor under study and with the disease outcome, and if the joint correlations are strong enough and if the fraction of the eligible subjects falling into those categories of non-participation is large enough, the respondents might provide a biased estimate of the true OR between exposure and disease. Thus all of those subgroups of non-respondents are relevant components of nonresponse and all of them should be documented. There is one exception however. By contrast with the other reasons, the inability to speak the local language criterion can be dispensed with by simply defining the study base in such a way as to exclude all people who do not speak the local language. This would require excluding them from case and control groups and from respondents and non-respondents. While limiting generalizability of a study's findings, it would not compromise internal validity. Because this is a legitimate strategy, we will consider that studies do not need to count non-participation due to language difficulty as a component of the denominator for computing response rates. The other reasons however, should be counted, and their absence will be noted.

Consequently, in order to keep the data extraction method uniform for our assessment on time trends of response rates in case-control studies of cancer, we adopted the following formula for the calculation of response rates:

$$ResponseRate = \frac{Total\ Particpants}{Eligible\ Subjects}$$

$$Eligible\ Subjects = Total\ Particpants + Subject\ Refusal + Subject\ Deceased\ or\ Too\ Ill + Subject\ Unreachable + Medical\ Source\ Obstacle(if\ applicable)$$

To the extent that the published papers provided the required data, we calculated response rates for each case and control series based on our formula presented above, and thus, the recorded response rates are not necessarily the same as the ones published by the investigators. When applicable, we also recorded whether studies treated non-respondents due to "medical source obstacles" as eligible. When studies did not provide sufficient information that allowed for a calculation of their response rates using the above formula, we recorded the rates reported by the authors.

Statistical analyses

We examined the time trends of response rates, separately for cases and each type of controls, using univariate linear regression models. Response rate (the outcome variable) was measured as the proportion of persons who participated, and time (the predictor variable) was measured as the mid-point year of data collection of each study, and was categorized into 4 time periods (1971-1980, 1981-1990, 1991-2000, 2001-2010); the period 1971-1980 was defined as the reference group. Time trends of each nonresponse rate (subject refusal, deceased or too ill, unreachable, and medical source obstacle(s)) were also examined using similar methodology. We also conducted sensitivity analyses using only self-respondent response rates, since the quality of interview conducted with proxies might be less reliable compared to that of self-respondents, which may result in information bias. To explore the yearly change in response

rates within each time period and subject series, we carried out regression analyses using a linear spline model. Potential study design determinants of response rate for each subject series were examined using a multivariate linear regression model; all of these potential determinants were considered as main independent variables and entered together into one multivariate model to be adjusted for each other and for time. Potential study design determinants of response rate included study population (North America / Northern Europe, or others), cancer type (only applicable for cases), mode of data collection (in-person, or others), type of respondent accepted (self only, proxy only, or self and proxy), and biologic sample collection (invasive, non-invasive, or none). We also describe the response rates as a function of the quality of reporting of response rates. The reporting quality index for each study was derived by a method described by Xu et al (2016) (47); it ranges from 0 (no information) to 3 (full information).

Tests of statistical significance were two sided, with an alpha level of 0.05. Statistical analyses were conducted using SPSS (IBM SPSS Statistics, Version 20.0. Armonk, NY: IBM Corp).

Results

We extracted information from 370 case-control studies of cancer (Figure 1) published during 1984-2013 from twelve journals of epidemiology, public health and general medicine (three journals were excluded due to a lack of published studies meeting our inclusion criteria); as shown in Table 1, one general epidemiology journal and three cancer journals accounted for nearly 80% of the sampled studies. Study's mid-point year of data collection ranged from 1961 to 2010, with 37% of them conducted during 1991-2000. 51 studies used multiple control series, yielding a total of 370 case series and 422 control series in our data. Of these control series, 66% were selected from the general population, 31% were selected from medical sources and 3%

were selected from friends and/or family of cases. Because such a small number of studies used friend or family controls, we did not include these in our analyses. The most examined cancer types in our surveyed studies were breast, cervix or endometrial cancers (22%), lung, mesothelioma or respiratory tract cancers (11%), and hematopoietic cancers (10%). Two-thirds of studies were conducted in North American populations with the rest spread in the other eligible regions. 69% of studies collected data from subjects in person, with the rest collected data via mail, telephone, or multiple methods combined. 80% of studies only interviewed subject respondents; most of the remaining accepted proxy response. Biologic samples were collected in 24% of studies; most of them collected samples via invasive methods (e.g. blood).

Table 2 shows the median and its 25 to 75 percentile range of subject response rates in surveyed case-control studies of cancer by study data collection period (not date of publication) and by each study design factor for cases, medical source controls and population controls, respectively. The overall median response rates were 77.2%, 86.8%, and 67.0%, for cases, medical source controls, and population controls, respectively, in studies conducted during 1971-2010. The recent levels of median response rates in studies conducted during 2001-2010 were 75.6%, 78.0%, and 53.0% for cases, medical source controls, and population controls, respectively. For all three subject series, response rates were highest before 1990, and declined in studies conducted after 2000. When restricted to studies that only used self-respondents (Appendix 1), we observed slightly lower but very similar pattern of response rates over time in all three subject series.

The non-response rate for each reason for non-participation is presented in Table 3. Reasons for non-participation were rarely reported in publications; the most reported reason was subject refusal and the least reported was medical source obstacles. Subject refusal accounted for

the most prevalent reason for non-participation for cases (9.6%) and population controls (21.5%), and the most prevalent reason for medical source controls was non-participation due to medical source obstacles (10.3%). However, we observed a change in how authors consider the eligibility of non-respondent cases due to medical source obstacles and in the reporting of this reason for non-participation (Table 5). Over time, fewer studies reported this reason for non-participation and even fewer considered these non-respondents as eligible.

Of the studies that reported having requested biologic samples from all participants, the collection rate was only reported in 41% of studies for cases, 37% for medical source controls, and 32% for population controls (Table 4). The median biologic sample collection rate was 72% for cases, 75% for medical source controls, and 52% for population controls. There was no obvious time trend of this rate except for a steep decline observed in medical source controls in studies conducted after 2000; however, very few studies conducted after 2000 adopted the use of medical source controls.

Table 6 presents the time trends of response rates from self and proxy respondents in our surveyed studies, by type of subject series. Overall, response rates declined over time. For cases, we observed a statistically significant change of -5.99% (95%CI: -11.50%, -0.48%) of response rate in 2001-2010, when compared to that in 1971-1980. For population controls, statistically significant changes of -11.07% (95%CI: -16.52%, -5.62%) and -17.04% (95%CI: -23.17%, -10.91%) were observed in 1991-2000 and in 2001-2010, respectively. No significant decline of response rate was observed in medical source controls. When analyses were restricted to studies that only included self-respondents (Appendix 2), we observed statistically significant and greater (except for population controls) declines of response rates in 2001-2010, in all subject

series. The yearly change in response rate (self and proxy) within each time period for each subject series are presented in Appendix 3.

Table 7 presents the time trends of each non-response rate. When compared to 1971-1980, we observed statistically significant increases of subject refusal rates in 2001-2010 for cases and medical source controls. Statistical significant increases in subject refusal were also observed in the periods 1991-2000 and 2001-2010 for population controls. In addition, when compared to 1971-1980, we also observed statistically significant declines of non-response rates due to subject being unreachable for medical source controls in the periods 1981-1990 and 1991-2000; however, these are likely due to chances since only 9 studies were included in those analyses. No obvious change in non-response rate was detected for other reasons.

Table 8 presents the association between each study design factor and the response rate, by type of subject series. Our data shows that the study design determinants for cases' participation included location of study population and mode of data collection. The only determinant of medical source controls' participation was location of study population, and the only determinant for population controls' participation was type of respondent accepted.

Discussion

Our results indicate that response rates in case-controls studies of cancer have declined over the past 30 years, and that this decline was steeper in studies conducted after 2000. There was a greater decline of response rate in control series than in cases series. Non-participation due to subject refusal has increased over time, especially in the population control series. We also observed a change in method of response rate calculation and in reporting of non-participation due to medical source obstacles for the case series. In addition, several study design factors, such

as cancer type, study population, mode of data collection, and type of respondent accepted, were shown to be the determinants of response rates.

Previous review of subject participation in epidemiologic studies (14) concluded that societal and lifestyle changes contributed greatly to the decline of response rates in scientific studies over the past decades. For example, the emergence of telemarketing and political polls reduced the general public's willingness to participate in scientific studies. Furthermore, longer working hours, and the increase in women joining the workforce also reduced subjects' availability to participate in scientific research (14). In view of the social and technological changes, epidemiologists have started to question the effectiveness of using some traditional survey methods (e.g. random-digit dialing) for epidemiologic research.

Since the 1990s concerns have been raised regarding the methods used to calculate and report response rates in published studies (20, 32). Previous assessments of response rate time trends in observational epidemiologic studies were severely impeded by a lack of reporting and a lack of consistency in the methods used to calculate response rates in published studies. A survey of researchers in the field of cancer case-control studies (20) concluded that there was a wide range of methods adopted to calculate response rates; moreover, it was difficult to verify whether the methods used to calculate this rate have changed over time since the quality of response rate reporting was and is still poor in published studies. In our data, a higher percentage of studies reported detailed information on response rates and reasons for non-participation in studies published in 1995 than in studies published after 2000, with only around 10% and 1% of studies providing sufficient information to allow for the calculation of response rate and non-response rate for each reason for non-participation for cases or population controls, and for medical source controls, respectively (data not shown).

We observed that with time, fewer studies reported non-participation of cases due to medical source obstacles and fewer considered these non-respondents eligible. There has been an increasing amount of restrictions imposed by ethical review bodies on researchers to access human subjects without medical personnel intercession (14, 25, 44). However, given that most medical personnel are already too occupied with their own tasks, it is problematic to rely on them to recruit participants for epidemiologic studies. In addition, the nature and quality of such intervention is not easily controllable by epidemiologists, thus this may lead to the losses of potential participants and of representative subject samples (42, 43). Given that, it is plausible to speculate that over time, researchers would report less non-participation due to medical source obstacles and/or exclude such non-respondents from the calculation to give the impression of higher response rates.

Very few studies examined the level of subject response rates in epidemiologic case-control studies. One study (20) compared the response rates of population controls in 2 studies conducted in the mid-1980s to 2 similar studies conducted in the late 1970s or early 1980s, and concluded that population controls' response rates had declined by 16-28%. Another study (33) demonstrated that in similar settings, the amount of researchers' efforts needed to maintain high response rate in population controls had almost doubled from 1991 to 2003. Previous reviews have examined the time trends of response rates in surveyed case-control studies conducted between 1970s to the early 2000s (16, 32, 34). Two reviews (16, 32, 34) concluded that no significant changes in response rates were observed in studies conducted until the late 1990s, and one review (16) concluded that significant declines of response rates in both cases (-1.18% per year) and controls (-1.49% per year) were observed in 107 case-control studies conducted from 1970-2003, with steeper but non-significant declines of response rates observed in studies

conducted from 1990-2003. One of the problems with earlier reviews is that they tended to rely on the authors' reported response rates. But as we argued, authors have not been consistent in their operational definitions and have tended to exaggerate their response rates by neglecting to include some categories of non-participants among the eligible. We attempted to minimize this problem by recalculating response rates based on standardized criteria. Even this attempt may not have fully succeeded since we sometimes had to accept authors' claims of their response rates because of the paucity of information for recalculating true response rates. We observed in our surveyed studies that the response rates seemed to be higher in studies with low quality of reporting. This might indicate that despite our attempts to recalculate true response rates in these studies, there was crucial information hidden from view in some publications and we were too generous in crediting the authors' claims of high response rates.

Our findings indicated that response rate did not change significantly from the 1970s to the 1990s, but that this rate only started to deteriorate significantly from the 2000s and the 1990s, for cases and for population controls, respectively. We did not observe a significant decline of response rates in medical source controls in studies conducted after 2000. As subject participation has declined precipitously for population controls but not for medical source controls, researchers should consider the merit of using medical source controls rather than population controls when planning new case-control studies of cancer.

Given the importance of response rate in case-control studies, it is essential to understand its determinants. Some potential determinants are individual level characteristics like age, sex and education; others are study design characteristics like the type of cancer being studied, the location of the study, and whether biological samples were solicited. By its nature our study was only capable of elucidating the role of study design variables.

Other investigations have demonstrated that several sociodemographic characteristics, such as sex, SES, education, health status, employment status, marital status, being exposed to the exposure of interest, and having the disease being examined, influence the likelihood of response (14, 16, 29) . However, researchers have no control over these characteristics and there was little evidence of strategies that can be applied to all epidemiologic studies to increase participation via targeting sociodemographic characteristics of the sampled population (14, 30). On the contrary, certain study design factors can be controlled by researchers and have been shown to be associated with the success in enrolling subjects in epidemiologic studies. Higher participation were observed in studies that adopted in-person or multiple methods of subject recruitment and data collection, that did not require substantial commitments or invasive procedures, and that provided incentives. In our data, we observed the highest response rates in studies that interviewed subjects in person; however, using multiple methods did not improve subject participation, nor did we observe a decline in interview response rate or in biologic sample collection rate in studies involving invasive data collection. The lack of association between biologic sample collection and subject participation may be explained by the fact that in our surveyed studies, subjects were not obligated to provide biologic samples in order to participate in the studies. We were not able to explore the influence of incentives on response rates since this information was provided in 2% of the surveyed studies. In addition to the aforementioned study design factors, we observed that additional factors, such as location of the study population and type of respondent accepted also influenced the response rates in case-control studies of cancer.

Compared to previous time trend analyses which included 26 to 82 surveyed case-control studies and covered study periods until the early 2000s, we were able to examine the time trends

and study design determinants of response rates in studies conducted between 1971 and 2010, in 370 surveyed case-control studies of cancer. Other than providing an updated review of the current level of response rate, our large sample size also allowed for the examination of reported reasons for non-participation and their change over time in each subject series. To account for inconsistencies in the methods used for response rate calculation in our surveyed studies, we recalculated subject response rate for each study based on standardized criteria; however, the lack of reporting of subject participation in surveyed studies made it difficult to calculate response rates in a uniform manner. Unspecified response rates and unreported reasons for non-participation can still lead to an overestimation (or an underestimation in rare occasions) of the real subject response rates due to residual confounding. As there is no current consensus in how response rate should be calculated and reported, we are aware that others may not agree with our definition of response rate; however, we believe that major sources of non-participation should be reported and included in the calculation to reduce the potential for nonresponse bias. Authors should provide sufficient and transparent disclosure on study participation and leave the readers the freedom to interpret the validity of a study.

Conclusion

Response rates of case-control studies of cancer have declined over the past 30 years and this decline is accelerating, which increases study's potential for selection bias. The decline is particularly dramatic among population controls, and it threatens the credibility of results derived from case-control studies of cancer.

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Tables, figure and appendices

TABLE 1. Frequency distributions of the surveyed studies

	No.	%
All	**370**	
Journal		
CEBP	83	22.4
AJE	71	19.2
CCC	68	18.4
IJC	63	17.0
Others[1]	85	23.0
Publication year		
1984-1986	75	20.3
1995	83	22.4
2005	140	37.8
2013	72	19.5
Cancer type		
Breast, cervix, endometrium	83	22.4
Lung, mesothelioma, respiratory tract	42	11.4
Hematopoietic	36	9.7
Prostate, testicle, penis	32	8.6
Head and neck	30	8.1
Colorectum	28	7.6
Bladder, kidney, urinary tract	27	7.3
Ovary	23	6.2
Stomach, liver, pancreas	22	5.9
Skin	16	4.3
Brain	15	4.1
Others	16	4.3
Study population		
North America (USA and Canada)	245	66.2
Southern Europe[2]	51	13.8
Northern Europe[3]	41	11.1
Eastern Europe[4]	8	2.2
Australia or New Zealand	16	4.3
Multiple	9	2.4
Median year of data collection		
1961-1980	63	17.0
1981-1990	103	27.8
1991-2000	138	37.3
2001-2010	59	15.9
Not mentioned	7	1.9
Type of control series[5]		
Population [6]	278	65.9
Medical source[7]	131	31.0
Friends and family	13	3.1
Mode of data collection		
In-person	256	69.2
Mail	36	9.7
Telephone	31	8.4
Multiple methods	43	11.6
Not mentioned	4	1.1
Type of respondent accepted		
Self only	297	80.3
Proxy only	6	1.6
Self and proxy	64	17.3
Not mentioned	3	0.8
Biologic sample collection		
Yes	87	23.5
Invasive	*64*	*73.6*
Non-invasive	*23*	*26.4*
No	283	76.5

1. All other journals listed in Figure 1, except for Prostate, Lung Cancer and Journal of Epidemiology and Community Health, which had no studies meeting the inclusion criteria.

2. Southern Europe: Spain, Portugal, Italy, Greece, France.

3. Northern Europe: Finland, Sweden, Norway, Denmark, Netherlands, including Germany and United Kingdom.

4. Eastern Europe: Russia, Poland, Czech Republic, Slovakia, Hungary, Romania, Bulgaria, Turkey, Slovenia.

5. The sum of the percentage of each type of control series do not add up to 100 because some studies used more than one type of control series.

6. Includes sources such as population registers, electoral lists, random digit dialing, driver's license, governmental medical insurance lists and neighbors of cases.

7. Includes such sources as hospital or clinic patients, HMO or GP lists, and cancer or death registers.

TABLE 2. Response rates in surveyed studies by type of subject series (case series, medical source control series, and population control series)

	Response Rates (%)											
	Cases				Medical source controls				Population controls			
	n	Median	25-75 percentile	*P-value (One-way ANOVA)	n	Median	25-75 percentile	P-value (One-way ANOVA)	n	Median	25-75 percentile	P-value (One-way ANOVA)
Total	311	77.2	68.0-86.0		71	86.8	75.0-95.7		241	67.0	54.0-75.5	
Data collection period				0.01				0.06				0.00
1971-2000[1]	258	78.2	69.0-86.2		64	87.9	75.0-96.0		195	69.0	58.2-76.6	
1971-1980	50	78.2	72.0-86.3		17	77.0	73.1-88.5		29	75.6	62.3-83.0	
1981-1990	82	79.5	70.0-88.0		18	95.0	77.0-97.2		66	74.1	68.6-82.6	
1991-2000	126	76.0	65.0-85.0		29	87.9	77.5-96.0		100	62.9	53.8-69.9	
2001-2010	51	75.6	60.2-79.5		5	78.0	50.8-86.6		46	53.0	46.6-67.3	
Cancer type				0.02								
Breast, cervix, endometrium	67	78.6	71.2-82.1									
Lung, mesothelioma, respiratory	30	83.4	73.1-86.3									
Hematopoietic	33	72.2	59.3-85.7									
Prostate, testicle, penis	28	75.8	69.2-80.1									
Head and neck	24	80.9	76.0-87.6									
Colorectum	24	70.5	65.0-83.3									
Bladder, kidney, urinary tract	23	73.7	70.0-86.7									
Ovary	22	71.7	60.3-76.8									
Stomach, liver, pancreas	20	68.4	57.0-89.8									
Skin	15	83.0	78.5-97.1									
Brain	12	83.3	70.2-88.5									
Study population				0.00				0.00				0.00
North America and Northern	250	76.0	67.0-82.5		36	75.1	63.5-88.8		216	67.0	55.3-75.1	
North America[2]	214	74.6	66.5-82.0		30	75.1	66.8-86.0		190	66.6	53.9-75.0	
Northern Europe [3]	36	79.1	74.3-88.0		6	77.5	55.3-92.3		26	71.0	66.8-76.7	
Others	61	89.0	77.8-96.2		35	95.0	86.0-97.0		25	58.3	44.3-77.0	
Southern Europe [4]	34	95.0	85.8-97.1		28	95.3	92.7-98.3		5	76.1	63.0-86.0	
Eastern Europe [5]	7	86.0	83.9-91.0		2	81.5	-		2	83.0	-	
Australia or New Zealand	15	64.3	58.1-79.8		2	78.6	-		13	45.9	41.1-67.9	
Multiple	5	91.3	77.9-91.8		3	86.0	-		5	58.2	52.5-69.7	
Mode of data collection				0.00				0.01				0.08
In-person	213	79.0	70.0-87.4		58	90.3	76.5-96.0		156	66.3	54.0-75.0	
Others	97	74.6	61.2-81.0		13	73.8	56.5-84.6		85	67.1	51.6-78.9	
Mail	30	67.4	55.7-79.1		5	60.0	48.8-91.0		21	63.3	41.1-73.8	
Telephone	28	80.3	70.1-85.8		3	80.0	-		29	71.0	59.9-83.5	
Multiple methods	39	73.0	63.5-83.5		5	63.9	58.2-79.9		35	67.0	51.0-76.6	
Type of respondent accepted				0.61				0.04				0.00
Self only	245	76.7	67.0-84.8		57	89.0	75.1-96.0		191	65.0	52.2-72.7	
Proxy only	5	74.0	59.8-90.8		4	82.0	55.7-94.4		0	-	-	
Self and proxy	60	80.8	69.9-87.0		10	78.4	62.9-86.8		50	75.1	67.0-83.0	
Biologic sample collection				0.78				0.76				0.13
Yes, invasive [6]	58	76.1	69.9-84.3		17	89.0	77.5-95.3		41	64.0	56.0-70.3	
Yes, non-invasive [7]	16	74.2	70.6-82.8		3	93.0	-		14	69.0	43.7-75.3	
No	237	78.5	67.0-86.1		51	85.3	74.1-96.0		186	67.9	54.0-77.0	
Journal				0.00				0.14				0.00
CEBP	70	76.6	70.0-84.1		17	87.9	67.2-95.8		49	66.0	55.5-73.1	
AJE	59	78.5	66.0-83.9		15	77.0	73.8-88.0		43	67.0	56.6-75.0	
CCC	60	73.6	63.5-80.7		8	89.1	76.0-98.0		58	56.0	45.4-69.1	
IJC	51	84.0	73.7-95.0		19	95.0	80.0-97.0		31	71.9	66.0-79.0	
Others [8]	71	79.0	66.7-86.0		12	82.1	69.3-93.9		58	71.4	58.5-78.2	
Response rate reporting score				0.00				0.07				0.79
1 [9]	148	79.1	71.2-88.0		43	81.0	73.8-95.0		154	67.0	54.0-76.0	
2 [10]	119	78.4	63.5-86.0		27	93.0	83.2-96.0		57	67.0	52.9-73.5	
3 [11]	44	73.0	60.5-76.8		1	63.4	-		30	65.1	49.4-76.4	

1. One study conducted in 1961 was removed from the descriptive and analytical analyses
2. North America: USA and Canada
3. Northern Europe: Finland, Sweden, Norway, Denmark, Netherlands, including Germany and United Kingdom
4. Southern Europe: Spain, Portugal, Italy, Greece, France

5. Eastern Europe: Russia, Poland, Czech Republic, Slovakia, Hungary, Romania, Bulgaria, Turkey, Slovenia
6. Invasive: blood sample collection
7. Non-invasive: urine, saliva, nail or hair sample collection
8. All other journals listed in Figure 1, except for Prostate, Lung Cancer and Journal of Epidemiology and Community Health, which had no studies meeting the inclusion criteria
9. Score 1: Information provided on eligible subjects and participants, but no information on reasons for non-participation
10. Score 2: Information provided on eligible subjects, participants, and some information on reasons for non-participation
11. Score 3: Comprehensive information on subject participation (provide information on participants and all 4 reasons for non-participation including subject refusal, medical source obstacle, subject deceased or too ill, and subject unreachable, so the number of eligible subjects could be calculated as the sum of participants and non-participants if it was not given explicitly)

* One-way analysis of variance (ANOVA) test: significance level of 0.05.

TABLE 3. Non-response rates in surveyed studies by type of subject series (case series, medical source control series, and population control series)

	Non-response rates (%)											
	Cases				Medical source controls				Population controls			
	No. of studies without relevant information	No. of studies with relevant information	Median	25-75 percentile	No. of studies without relevant information	No. of studies with relevant information	Median	25-75 percentile	No. of studies without relevant information	No. of studies with relevant information	Median	25-75 percentile
Refusal	239	131	9.6	5.0-13.6	102	29	5.0	4.0-10.0	200	78	21.5	14.4-28.9
Deceased or too ill	262	108	8.0	4.1-14.0	123	8	3.1	0.9-5.8	237	41	2.0	1.0-4.3
Unreachable	279	91	4.0	2.0-7.0	122	9	6.0	2.4-8.1	218	60	7.4	3.1-13.0
Medical source obstacle*	279	85	5.9	3.0-10.0	121	4	10.3	4.6-14.0				

*Not applicable (only proxy respondents of deceased subjects were interviewed) in 6 studies for cases and in 6 studies for medical source controls.

TABLE 4. Biologic sample collection rates in surveyed studies that requested biologic samples, by type of subject series (case series, medical source control series, and population control series)

	Biologic Sample Collection Rates (%)											
	Cases				Medical source controls				Population controls			
Data collection period	No. of studies without relevant information	No. of studies with relevant information	Median	25-75 percentile	No. of studies without relevant information	No. of studies with relevant information	Median	25-75 percentile	No. of studies without relevant information	No. of studies with relevant information	Median	25-75 percentile
Total	49	34	72.0	60.0-87.0	17	10	75.0	69.4-98.0	45	21	52.2	47.0-67.8
1971-2000	36	29	69.1	60.2-83.6	16	9	91.0	70.2-99.0	33	18	52.5	48.3-66.9
1971-1980	2	1	100	-	1	1	100	-	0	0	-	-
1981-1990	7	4	81.4	70.5-97.0	0	3	98.0	-	5	2	76.3	-
1991-2000	27	24	64.4	56.6-77.9	15	5	73.0	70.2-94.4	28	16	52.2	48.1-65.5
2001-2010	13	5	77.8	50.9-91.0	1	1	45.9	-	12	3	42.3	-

TABLE 5. Proportion of surveyed studies that considered "medical source obstacles" as an eligibility criterion for case recruitment, by data collection time period

	Count as eligible		Count as ineligible		Lack of / insufficient information	
	No.	% (by time period)	No.	% (by time period)	No.	% (by time period)
Total	86	24.2	23	6.5	247	69.4
1971-1980	15	25.4	2	3.4	42	71.2
1981-1990	33	33.0	1	1.0	66	66.0
1991-2000	31	22.5	14	10.1	93	67.4
2001-2010	7	11.9	6	10.2	46	78.0

TABLE 6. Time trends of response rate in surveyed studies in which data were collected from 1971-2010, by type of subject series (case series, medical source control series, and population control series)

	Cases			Medical source controls			Population controls		
Data collection period	Difference (%) in response rate from 1971-1980	95% CI	P value	Difference (%) in response rate from 1971-1980	95% CI	P value	Difference (%) in response rate from 1971-1980	95% CI	P value
1981-1990	1.74	-3.24, 6.72	0.49	9.17	-1.42, 19.76	0.09	0.35	-5.41, 6.11	0.90
1991-2000	-2.50	-7.13, 2.12	0.29	8.13	-1.30, 17.56	0.09	-11.07	-16.52, -5.62	0.00
2001-2010	-5.99	-11.50, -0.48	0.03	-7.10	-22.80, 8.61	0.37	-17.04	-23.17, -10.91	0.00

Model: Subject response rate (%) = b0 + b1 x data collection period

b1: Difference (%) in response rate of each time period from 1971-1980

Reference group for data collection period: 1971-1980

TABLE 7. Time trends of non-response rates in surveyed studies in which data were collected from 1971-2010, by type of subject series (case series, medical source control series, and population control series)

	Non-response Rates (%)								
	Cases			Medical source controls			Population controls		
Data collection period	Difference (%) in response rate from 1971-1980	95% CI	P value	Difference (%) in response rate from 1971-1980	95% CI	P value	Difference (%) in response rate from 1971-1980	95% CI	P value
Non-response due to subject refusal									
1981-1990	-0.19	-3.68, 3.30	0.91	-5.64	-14.68, 3.39	0.21	2.48	-3.99, 8.95	0.45
1991-2000	0.65	-2.61, 3.90	0.70	-5.01	-11.43, 1.42	0.12	11.93	5.41, 18.45	0.00
2001-2010	3.95	0.03, 7.87	0.05	14.14	2.39, 25.89	0.02	10.84	3.64, 18.05	0.00
Non-response due to subject deceased or too ill									
1981-1990	-4.54	-9.43, 0.35	0.07	-3.38	-11.92, 5.16	0.36	-4.67	-9.86, 0.52	0.08
1991-2000	-1.58	-6.05, 2.89	0.49	-0.06	-5.89, 5.77	0.98	-2.29	-6.99, 2.42	0.33
2001-2010	-3.95	-9.39, 1.48	0.15	-	-	-	-3.08	-8.37, 2.21	0.25
Non-response due to subject unreachable									
1981-1990	-1.20	-3.64, 1.24	0.33	-6.54	-12.19, -0.88	0.03	-5.23	-10.99, 0.52	0.07
1991-2000	-1.92	-4.13, 0.29	0.09	-6.66	-12.31, -1.01	0.03	-1.03	-6.28, 4.22	0.70
2001-2010	-0.80	-3.55, 1.94	0.56	-	-	-	-3.16	-9.59, 3.27	0.33
Non-response due to medical source obstacles*									
1981-1990	1.13	-3.66, 5.92	0.64	-	-	-			
1991-2000	-0.87	-5.40, 3.66	0.70	-	-	-			
2001-2010	-0.43	-6.76, 5.91	0.89	-	-	-			

Models: For all models, the data collection period of 1971-1980 was used as the reference group.
Subject refusal (%) = b0 + b1 x data collection period
Subject deceased or too ill (%) = b0 + b1 x data collection period
Subject unreachable (%) = b0 + b1 x data collection period
Medical source obstacles (%) = b0 + b1 x data collection period

b1 represents the difference (%) in response rate of each data collection period from the period of 1971-1980.
* Insufficient data for time trend analysis of non-response due to medical source obstacles in medical source controls.

TABLE 8. Statistical significance of the contribution of each factor as a determinant of response rates, by type of subject series (case series, medical source control series, and population control series)

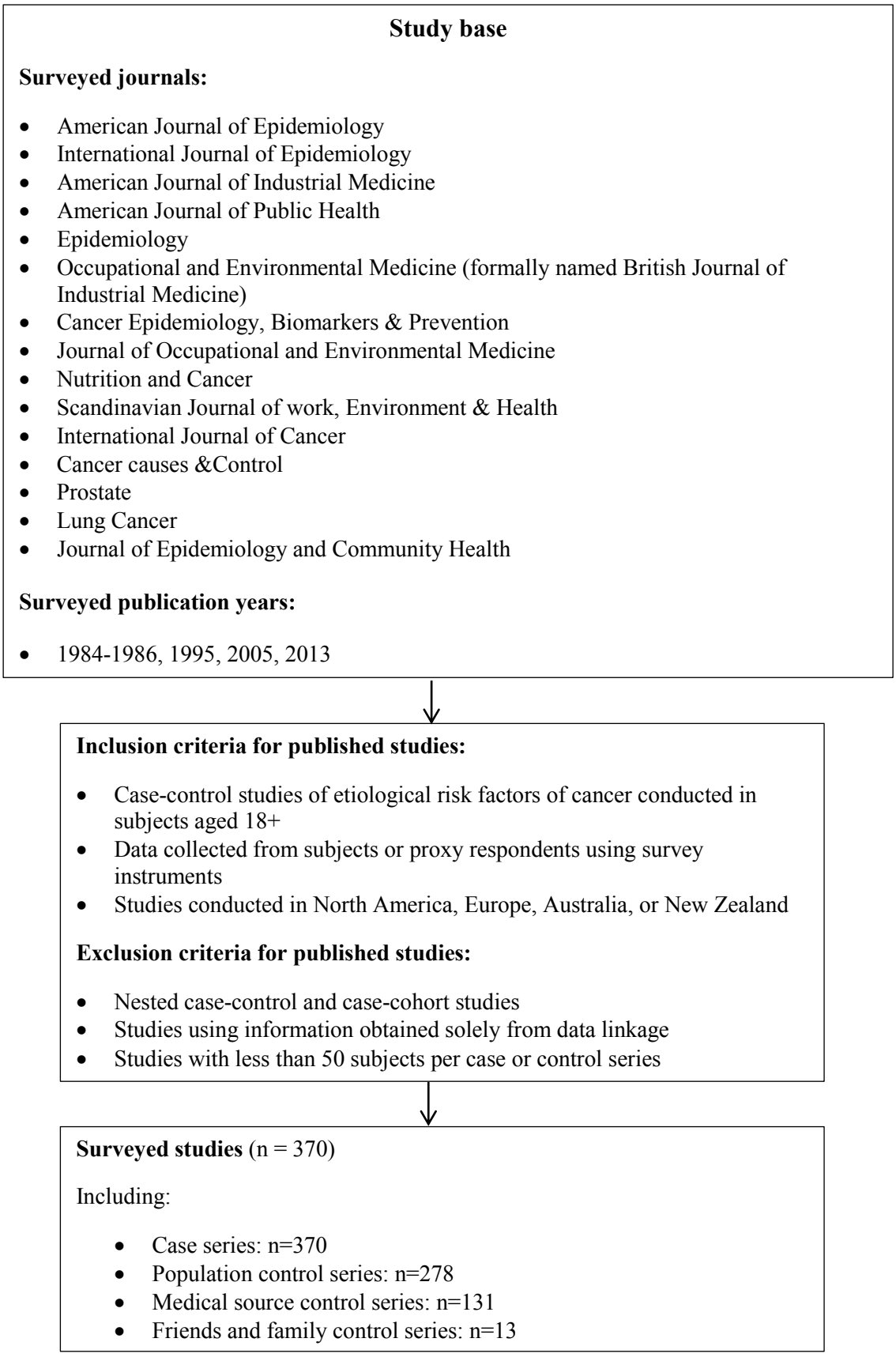
	Cases		Medical source controls		Population controls	
Study design factors [1]	ß[2]	95% CI for ß	ß	95% CI for ß	ß	95% CI for ß
Percentage of response rate (Constant)[3]	77.15	72.16, 82.14	77.68	69.65, 85.71	69.33	64.19, 74.46
Cancer type (Ref: Breast, cervix, endometrium cancers)						
Hematopoietic	-1.85	-7.65, 3.95				
Ovary	-5.10	-11.43, 1.23				
Prostate, testicle, penis	-1.34	-7.12, 4.44				
Lung, mesothelioma, respiratory tract	-0.72	-6.66, 5.23				
Stomach, liver, pancreas	-5.78	-12.58, 1.02				
Colorectum	-5.36	-11.56, 0.84				
Bladder, kidney, urinary tract	-0.84	-7.33, 5.64				
Head and neck	2.88	-3.48, 9.24				
Brain `	6.33	-2.42, 15.08				
Skin	6.11	-1.17, 13.39				
Others	5.34	-2.97, 13.65				
Study population (Ref: North American and Northern European populations)						
Other populations	11.80*	7.92, 15.68	16.76*	9.31, 24.21	-0.97	-6.55, 4.61
Mode of data collection (Ref: In-person)						
Other modes of data collection	-4.78*	-8.18, -1.38	-5.50	-15.87, 4.88	0.74	-2.82, 4.29
Type of respondent accepted (Ref: Self only)						
Proxy only	0.86	-11.30, 13.02	-2.47	-17.13, 12.18	-	-
Self and proxy	1.75	-2.60, 6.09	-4.37	-16.12, 7.37	7.39*	3.15, 11.62
Biologic sample collection (Ref: Bio sample not collected)						
Invasive	3.34	-0.87, 7.56	3.88	-4.48, 12.23	2.189	-2.63, 7.01
Non-invasive	2.88	-4.02, 9.79	5.86	-10.83, 22.54	-2.72	-9.96, 4.52

1. Regression models adjusted for all presented variables and data collection period (1971-1980, 1981-1990, 1991-2000, 2001-2010).

2. The ßs represent the percentage change in response rate for studies in the selected category when compared to the reference category, adjusted for the remaining variables.
3. The constant represents the response rate for studies with the reference category for each variable.

*= significant results

FIGURE 1. Surveyed study selection method



APPENDIX 1. Self-respondent response rates in surveyed studies by type of subject series (case series, medical source control series, and population control series)

	Self-respondent Response Rates (%)								
	Cases			Medical source controls			Population source controls		
	n	Median	25-75 percentile	n	Median	25-75 percentile	n	Median	25-75 percentile
Total	286	75.5	63.4-83.9	64	87.2	74.3-96.0	211	64.0	52.0-73.0
Data collection period									
1971-2000[1]	235	75.0	63.5-84.0	57	87.9	74.6-96.0	171	66.0	56.0-74.2
1971-1980	40	73.7	54.0-84.9	14	75.1	31.1-88.3	22	73.8	56.0-83.0
1981-1990	75	76.0	63.4-84.0	14	95.8	90.4-98.5	54	72.0	65.5-80.0
1991-2000	120	74.6	64.5-84.0	29	87.6	77.1-96.0	95	62.4	52.8-69.0
2001-2010	49	75.5	60.2-79.1	5	78.0	50.8-86.6	40	52.1	44.0-67.0
Cancer type									
Breast, cervix, endometrium	65	79.0	70.7-82.4						
Lung, mesothelioma, respiratory	26	71.6	52.5-84.3						
Hematopoietic	31	72.2	58.8-83.8						
Prostate, testicle, penis	26	75.0	64.1-80.9						
Head and neck	22	78.0	59.8-87.6						
Colorectum	23	71.0	65.0-84.0						
Bladder, kidney, urinary tract	17	76.0	69.5-89.5						
Ovary	22	71.7	60.3-76.8						
Stomach, liver, pancreas	16	64.0	35.8-84.0						
Skin	15	83.0	78.5-97.1						
Brain	10	73.0	21.4-81.3						
Study population									
North America and Northern Europe	230	73.1	62.0-80.5	31	75.0	57.0-87.6	190	64.8	53.0-73.1
North America [2]	201	72.0	61.2-79.0	28	75.0	60.4-87.0	169	63.3	52.1-72.4
Northern Europe [3]	29	79.1	73.8-88.6	3	57.0	-	21	71.0	64.7-75.1
Others	56	87.6	76.7-96.0	33	95.0	86.0-97.9	21	58.2	41.9-74.0
Southern Europe [4]	32	95.0	85.7-97.0	27	95.0	92.1-98.8	4	74.0	58.5-83.8
Eastern Europe [5]	7	84.1	80.4-91.0	2	81.5	-	1	78.6	-
Australia or New Zealand	13	63.5	57.9-77.8	1	74.1	-	12	44.3	41.1-63.9
Multiple	4	89.8	87.4-92.0	3	81.0	-	4	59.4	53.6-73.7
Mode of data collection									
In-person	203	77.2	66.0-87.0	56	90.3	77.3-96.0	137	64.0	53.4-73.1
Others	83	70.0	58.1-79.1	8	50.3	30.5-71.2	74	63.1	47.8-73.0
Mail	23	71.0	57.7-79.1	1	47.6	-	19	62.5	41.1-67.1
Telephone	24	67.4	35.7-80.5	2	30.8	-	24	68.1	51.2-84.1
Multiple methods	36	71.0	60.5-76.0	5	63.4	38.0-76.5	31	62.5	50.1-71.1
Type of respondent accepted									
Self only	245	76.7	67.0-84.8	57	89.0	75.1-96.0	191	65.0	52.2-72.7
Self and proxy	41	58.4	31.2-72.7	7	31.4	23.0-79.2	20	60.2	39.4-79.5
Biologic sample collection									
Yes, invasive [6]	56	76.0	69.3-84.8	17	89.0	77.5-95.3	39	64.0	43.6-75.5
Yes, non-invasive [7]	16	72.8	69.4-81.1	3	93.0	-	13	69.0	11.0-79.8
No	214	75.2	60.9-83.8	44	85.3	74.0-96.0	159	64.0	52.0-73.8
Journal									
CEBP	67	76.0	69.1-84.0	17	87.9	67.2-95.8	45	65.0	52.5-71.3
AJE	54	69.5	60.3-82.0	13	75.0	47.4-82.4	37	63.0	53.5-74.6
CCC	56	72.8	60.5-80.3	7	92.1	79.2-99.0	51	55.0	45.3-67.0
IJC	49	83.0	73.4-95.0	19	95.0	80.0-97.0	29	71.8	64.5-78.8
Others [8]	60	72.9	58.1-81.9	8	83.2	74.3-97.3	47	65.0	52.0-73.8
Response rate reporting score									
1 [9]	137	77.2	67.5-85.4	39	81.0	74.1-95.7	132	65.0	53.0-74.1
2 [10]	109	73.7	60.0-84.8	24	94.0	79.0-96.0	53	64.6	46.4-72.8
3 [11]	40	73.6	60.1-78.0	1	63.4	-	26	60.3	46.7-71.9

1. One study conducted in 1961 was removed from the descriptive and analytical analyses
2. North America: USA and Canada
3. Northern Europe: Finland, Sweden, Norway, Denmark, Netherlands, including Germany and United Kingdom
4. Southern Europe: Spain, Portugal, Italy, Greece, France
5. Eastern Europe: Russia, Poland, Czech Republic, Slovakia, Hungary, Romania, Bulgaria, Turkey, Slovenia
6. Invasive: blood sample collection
7. Non-invasive: urine, saliva, nail or hair sample collection
8. All other journals listed in Figure 1, except for Prostate, Lung Cancer and Journal of Epidemiology and Community Health, which had no studies meeting the inclusion criteria
9. Score 1: Information provided on eligible subjects and participants, but no information on reasons for non-participation
10. Score 2: Information provided on eligible subjects, participants, and some information on reasons for non-participation

11. Score 3: Comprehensive information on subject participation (provide information on participants and all 4 reasons for non-participation including subject refusal, medical source obstacle, subject deceased or too ill, and subject unreachable, so the number of eligible subjects could be calculated as the sum of participants and non-participants if it was not given explicitly)

APPENDIX 2. Time trends of response rate in surveyed studies that only included self-respondents and in which data were collected from 1971-2010, by type of subject series (case series, medical source control series, and population control series)

	Cases			Medical source controls			Population controls		
Data collection period	Difference (%) in response rate from 1971-1980	95% CI	P value	Difference (%) in response rate from 1971-1980	95% CI	P value	Difference (%) in response rate from 1971-1980	95% CI	P value
1981-1990	-1.32	-7.36, 4.73	0.67	6.19	-4.39, 16.77	0.25	5.08	-2.07, 12.24	0.16
1991-2000	-4.77	-10.26, 0.72	0.09	0.77	-8.40, 9.94	0.87	-5.35	-12.02, 1.31	0.12
2001-2010	-9.67	-16.12, -3.22	0.00	-14.33	-28.39, -0.26	0.05	-12.35	-19.70, -4.99	0.00

Model: Self-respondent response rate (%) = b0 + b1 x data collection period

b1: Difference (%) in response rate from 1971-1980

Reference group for data collection period: 1971-1980

APPENDIX 3. Yearly change of response rate within each time period in surveyed studies in which data were collected from 1971-2010, examined using a linear spline regression model, by type of subject series (case series, medical source control series, and population control series)

Model [1]	Cases			Medical source controls			Population controls		
Data collection period	β [2]	95% CI	P value	β	95% CI	P value	β	95% CI	P value
1971-1980	0.90	-0.97, 2.77	0.34	3.32	-0.08, 6.73	0.06	0.20	-2.31, 2.70	0.88
1981-1990	-1.40	-3.75, 0.95	0.24	-3.68	-8.23, 0.87	0.11	-0.76	-3.80, 2.27	0.62
1991-2000	0.47	-0.67, 1.61	0.42	0.47	-2.13, 3.07	0.72	-0.40	-1.64, 0.85	0.53
2001-2010	-1.50	-3.03, 0.03	0.05	-5.68	-10.23, -1.13	0.02	-0.67	-2.21, 0.87	0.40

1. Regression spline models: response rate (%) = b0 + b1 x X1 + b2 x X2 + b3 x X3 + b4 x X4
   - X1= median year of data collection (continuous variable)
   - X2= X1-1981 if X1 ≥1981, 0 otherwise
   - X3= X1-1991 if X1 ≥1991, 0 otherwise
   - X4= X1-2001 if X1 ≥2001, 0 otherwise
2. The β regression coefficient represents the yearly change in response rate (%) in each data collection period.

6 Discussion

Overall, the quality of reporting of response rates and reasons for non-participation was very poor, especially for control series. Subject participation in case-control studies of cancer has declined over the past 30 years, and this decline was steeper in studies conducted after 2000.

Quality of reporting of response rates

As presented in manuscript 1, there was a rather poor reporting of relevant information on subject response rates in case-control studies of cancer, especially regarding reasons for non-participation. In addition, subject eligibility criteria were often unclear. Although the proportion of studies not reporting any information on response rates has declined slightly over time, overall reporting quality did not seem to have improved substantially. There was a tendency for better quality of reporting in case series, followed by population control series, and lastly by medical source control series.

It seems that many authors did not have a clear understanding of the distinction between "response rate", "participation rate", and "cooperation rate", as the terms were often used interchangeably. This problem is particularly apparent in studies for which full subject eligibility could not be ascertained at the initial stage, such as in studies using random digit dialing. While it is reasonable to exclude ineligible subjects from the denominator of response rate; it is, however, difficult to define correctly and consistently "eligibility" and the consequence of it can be detrimental. As Nattinger et al. (44) demonstrated, changing the definition of "eligible subject" could modify their subject

response rate from 57% to 70%. In the context of case-control studies of cancer where the sampling frame usually differs between case and control series, poorly or incorrectly defined eligibility criteria for cases and controls could cause an unpredictable level of selection bias, despite a reported high response rate.

Reviews carried out in the early 2000s reported that about half of the case-control studies provided no information regarding their response rates (16) (50) , whereas similar to our finding, a more recent review of survey research reported fewer studies without any information on response rates (51). Our estimates of the numbers of studies with very poor information ranged from about 12% among population control series to 45% among medical source control series. However, these reviews are not directly comparable because they covered different diseases, different topics, different populations and different eras. Unlike the other reviews, we also reviewed and extracted information on study participation from previous methodological publications of our surveyed studies. In any case, even the most favorable of these estimates is not encouraging. There are too many published studies with almost no useful information on response rates.

We observed that the quality of reporting seemed to peak in our 1995 sample. We also observed that since then, fewer studies reported non-participation of cases due to medical source obstacles and fewer considered these non-respondents eligible. We conjecture that the quality of response rate reporting improved up to that point because of increasing awareness of the importance of response rate as a contributor to study quality, and it declined afterwards because of a decrease in civic participation in general, increasing saturation with various types of solicitations and the increasing obstacles and "protections" imposed by ethics review authorities in accessing subjects, resulting in a

greater reluctance to reveal the true response rates to journal editors and reviewers, coupled with increasing pressure on word counts.

Time trends and study design determinants of response rates

As presented in manuscript 2, our results indicate that response rates in case-controls studies of cancer have declined over the past 30 years, and that this decline was steeper in studies conducted after 2000. There was a greater decline of response rate in control series than in cases series. Non-participation due to subject refusal has increased over time, especially in the population control series.

Very few studies examined the level of subject response rates in epidemiologic case-control studies. Previous reviews have examined the time trends of response rates in surveyed case-control studies conducted up to the early 2000s (16, 32, 34). Two reviews (16, 32, 34) concluded that no significant changes in response rates were observed in studies conducted until the late 1990s, and one review (16) concluded that significant declines of response rates in both cases and controls were observed in case-control studies conducted from 1970-2003. Our findings indicated that response rate did not change significantly from the 1970s to the 1990s, but that this rate only started to deteriorate significantly from the 2000s and the 1990s, for cases and for population controls, respectively. We did not observe a significant decline of response rates in medical source controls in studies conducted after 2000.

Given the importance of response rate in case-control studies, it is essential to understand its determinants. By its nature our study was only capable of elucidating the role of study design variables on subject participation. We observed the highest response

rates in studies that interviewed subjects in person; however, using multiple methods did not improve subject participation, nor did we observe a decline in interview response rate or in biologic sample collection rate in studies involving invasive data collection. The lack of association between biologic sample collection and subject participation may be explained by the fact that in our surveyed studies, subjects were not obligated to provide biologic samples in order to participate in the studies. We were not able to explore the influence of incentives on response rates since this information was provided in 2% of the surveyed studies. In addition to the aforementioned study design factors, we observed that additional factors, such as location of the study population and type of respondent accepted, also influenced the response rates in case-control studies of cancer.

Strength and Limitations

To our knowledge, our review included the largest sample of questionnaire-based case-control studies of cancer published in the past three decades, which enabled us to explore in great detail the current and past practice of reporting of response rates. However, there are a few considerations that may affect the interpretation of our study. First, as there is no consensus in how response rate should be calculated and reported, some may think that our definition is too conservative or rigid. Second, we reviewed articles from 15 journals that in our view were likely to have published a large fraction of epidemiological case-control studies of cancer. There have been other journals, but from an initial review these would not have accounted for large numbers of articles of the types we were searching for. Furthermore, the journals we selected probably represent the "best case scenarios" of high quality epidemiology journals; the quality of reporting of

response rates and the level of subject participation in studies published in other journals may be even lower.

It is possible that some reported response rates were biased in our sampled studies; due to the decline in subject participation, studies, especially more recent ones, could tend to report and calculate their response rates in more favorable methods. We attempted to minimize this problem by recalculating response rates based on standardized criteria, although this attempt may not have fully succeeded since we sometimes had to accept authors' claims of their response rates because of the paucity of information. But as we argued, authors have not been consistent in their operational definitions and have a tendency to exaggerate their response rates by neglecting to include some categories of non-participants among eligible subjects. We observed in our surveyed studies that the response rates seemed to be higher in studies with low quality of reporting. This might indicate that despite our attempts to recalculate true response rates in these studies, there was crucial information hidden from view in some publications. In our view, there is little probability of selection bias in our study since we reviewed and selected every article that was published in the selected years and journals. There is little evidence to believe that response rates and its reporting in articles published from other years during the past three decades would differ meaningfully from those reported in our selected samples. We do not intend to generalize our findings to other case-control studies of cancer conducted and published in other periods nor do we intend to infer our findings to studies conducted on other study populations.

6 Conclusion

Our study and previous literature on the topic of response rates in epidemiologic studies observed a decline in subject participation over the past decades and a generally poor quality of reporting for this methodological factor in published studies. Although low response rate itself does not infer low study validity, studies with low level of subject participation have a greater chance for selection biases when compared to studies with high level of participation. However, due to the inconstant methods of reporting for response rate in published studies, it is very difficult for readers to understand and to assess the validity of each study. Consequently, epidemiologists and public health practitioners should be cautious about this problem as biased results could influence scientific interpretations and decision making in public health.

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8 Appendix 1

Examples of the definitions of response rates, cooperation rates and participation rates from different sources.

Terms used to address subject participation	Definitions
Response Rate	• The percentage of people interviewed of those who were selected and eligible for the study (Slattery et al(20)). • The number of completed or returned survey instruments (questionnaires, interviews, etc.) divided by the total number of persons who would have been surveyed if all had participated (A dictionary of epidemiology(1)). • The number of complete interviews with reporting units divided by the number of eligible reporting units in the sample (AAPOR(21)).
Cooperation Rate	• The percentage of people interviewed of those who were contacted (Slattery et al(20)). • The proportion of all cases interviewed of all eligible units ever contacted (AAPOR(21)).
Participation Rate	• This term is used broadly, to refer to either “response rates” or “cooperation rates” (Morton et al (16)).