LETTERS TO THE EDITOR

Induced abortion as an independent risk factor for breast cancer

SIR—In a recent paper Brind *et al*[1] investigated the relationship between abortion and breast cancer in a so called meta-analysis. They used data from published reports to investigate whether induced abortion increases the risk of breast cancer. Their stated aim was to ascertain and quantify this risk. However, there are several methodological weaknesses in this analysis which bring into question their conclusions.

Firstly, the authors included only papers that have been published. It is well known and often discussed[2] that publication bias poses a crucial problem for the interpretation of results from meta-analysis. Papers reporting a positive effect are more readily published than papers showing no effect. Additionally, in most epidemiological studies, data are collected on many variables but they are only published in a selective way. Data on suspected risk factors tend to be published if results are striking. The authors briefly discuss this problem, but they argue that due to the "politically and legally ... sensitive" topic, publication is not biased towards a positive association with breast cancer incidence—rather towards a negative one! This argument is untenable. It seems to be motivated by a strong belief held by the authors but not by any scientific reasoning.

Secondly, the authors performed a literature search with *Medline*. It is well known that this is not even sufficient to obtain all published papers. Further work would be necessary for a comprehensive review—eg to search the references of published papers, to contact researchers, and to search through proceedings and abstracts of meetings. The authors used three specific key terms only; namely "abortion", "breast", and "cancer" in their *Medline* search. Papers with negative results on abortion might not use the term "abortion" in the title or in the abstract if the results were not the major findings. Other papers might use other terms such as *neoplasm, pregnancy, mammary carcinoma*. These articles would not have been located by their procedure. The literature search would thus have been strongly biased towards papers that mentioned abortion in the abstract, in effect identifying mainly papers where abortion had a "significant" effect.

Apart from English papers, the authors included Japanese, Portuguese, and Russian papers. No justification for this specific selection was made. Were there no publications in French, German, or Chinese?

The inclusion criteria were not clearly laid out. Although the authors stated in the text that publications after 1966 were included, both tables (table 1 and 2)[1] also included papers that appeared in 1960 and in 1957, suggesting possible selection by the authors.

Selection bias was most apparent with regard to the first reference, a study that should not have been included because it appeared in 1957 before the time period being considered. In addition, odds ratios were not given in the report of the study and the authors went out of their way to perform a quite complicated calculation to estimate an odds ratio. The inclusion of this study influenced the results towards achieving a positive association.

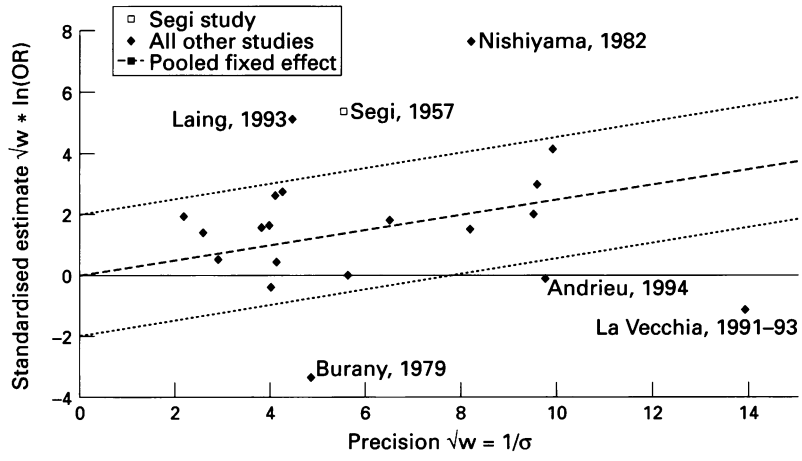

Figure 1 Induced abortion and breast cancer—radial plot. The figure is produced with data from table 1 of the paper of Brind et al[1] *excluding the studies of Pike* et al *1981*[1] *and Ewertz* et al *1988*[1]

To quantify the risk of breast cancer associated with induced abortion, the authors calculated a weighted average and an unweighted average of the odds ratios. No investigation of heterogeneity was performed before combining the data. In case of heterogeneity, a pooled estimator should not be calculated. We performed a test of homogeneity and found that the heterogeneity between studies was highly significant ($p<0.001$). This is a contraindication for estimating a pooled odds ratio (see fig 1, radial plot[1]). Six out of 21 studies gave an odds ratio outside the prediction limits around the pooled estimate. Two out of three "positive" outlying studies were from Japan, while the larger and more recent studies (references 67 and 61[1]) showed estimates far below the pooled odds ratio.

Odds ratios included in the calculation of a "pooled estimate" were derived in very different ways. Five studies reported only raw (crude) odds ratios. In several other studies, however, odds ratios were calculated using statistical regression models, adjusted for different confounding factors in multivariate analysis. The combination of crude and model based odds ratios may yield biased results. In addition to this, the reference group (women with no pregnancy or women with any pregnancy) was not consistent in all studies.

Differences between the studies with regard to study design, data collection, and statistical modelling were not presented in a systematic way. The possible influence of the choice of controls and of the method of data collection (questionnaire, interviews) was not discussed. It would have been instructive to perform the analysis separately for the different types of studies.

The description of the individual studies is in part overly extensive, but not aimed at bringing out the differences. After reading the introduction and the discussion we gained the impression that the authors had a very distinct opinion about the subject. All the papers in which positive results were obtained and cautiously interpreted by the communicating authors, were negatively reviewed by Brind *et al.*

The results of this meta-analysis seem to be strongly biased towards a positive effect—mainly due to the way studies were selected. Standard statistical methods that are available for meta-analysis (see, for example,[2]), in particular for the investigation of heterogeneity, were not used. We feel that it is unethical and harmful to publish such data as definitive results or facts of "meta-analysis" from observational studies when only a pooled estimate (with 95% confidence interval) is calculated, without investigating the heterogeneity between studies. Results from meta-analysis are often used and cited for further research and for implementing public health policies. In general, meta-analysis using only published data from epidemiological (observational) studies and not the original data set should be treated with caution. Some authors even argue that such a meta-analysis cannot yield reliable results in the presence of heterogeneity.

The conclusions drawn in the work of Brind *et al* are not based on a methodologically sound investigation and are therefore not justified.

MARIA BLETTNER
JENNY CHANG-CLAUDE
THOMAS SCHEUCHENPFLUG
German Cancer Research Centre, Division of Epidemiology, 69120 Heidelberg, Germany

1 Brind J, Chinchilli VM, Severs WB, Summy-Long J. Induced abortion as an independent risk factor for breast cancer: a comprehensive review and meta-analysis. *J Epidemiol Community Health* 1996;**50**:481–96.
2 Dickersin K, Berlin JA. Meta-analysis: state-of-the-science. *Epidemiol Rev* 1992; **14**:154–76.

Reply

We welcome substantive criticism of our "Comprehensive review and meta-analysis"[1] and the opportunity to respond to Blettner *et al*, although we vigorously dispute their objections.

First, they largely conclude that our results appear "strongly biased towards a positive effect—mainly due to the way studies are selected for the meta-analysis". To support this contention of "selection bias," they cite inclusion criteria that are simply not to be found in our paper. Nowhere did we limit our inclusion to papers published only since 1966, which is the earliest year that the *Med-*

line data base covers. On the contrary, our "searching (of) bibliographies of original studies and review papers" was clearly stated under "Search Methods".

Yet Blettner *et al* carry this line of criticism still further, claiming that selection bias was most apparent with the first reference (Segi *et al*, 1957[2]), firstly, because it was published before 1966 (see above), and, secondly, because its results were not given as odds ratios, and therefore we "went out of (our) way to perform a quite complicated calculation to estimate an odds ratio". However, since Segi *et al*, gave the total number of cases and controls and the fates of all pregnancies among them, an odds ratio could be calculated, providing the induced abortion exposure rates among women who had any abortions were available, so that the numbers of artificially aborted pregnancies could be translated into numbers of patients and controls. Since induced abortion exposure rates were available from two other Japanese studies, one based on an earlier,[3] and the other on a subsequent data base,[4] and since these figures were in close agreement, we applied the means of the exposure rates from the other two studies to the Segi study. Thus, by simply dividing the numbers of pregnancies artificially terminated in the Segi population by these mean exposure rates, the numbers of case and control subjects with any induced abortions were estimated and the odds ratio calculated. We do not consider such elementary arithmetic "quite complicated".

Yet still further along the "selection bias" trail, our critics from Heidelberg decry our lack of "justification" for the "specific selection" of "Japanese, Portuguese, and Russian papers," as if we had excluded "publications in French, German, or Chinese". Two points are noteworthy here. Firstly, they do *not* criticise us for our *inclusion* of a 1979 study in Serbo-Croatian,[5] a study which stands out as the *only* study to show an unequivocal *negative* association. Secondly, they do not cite a single study which we failed to include, thus providing the perfect refutation for their own claims that we were selective and that our search methods were "not sufficient".

One additional absurdity regarding "selection bias" stands out. Blettner *et al* claim that our "inclusion criteria were not clearly laid out". One simply wonders what is not clear about: "The single exclusion criterion is the absence of data relating specifically to induced abortion".

Another criticism of the meta–analysis brought by Blettner *et al* is of "publication bias," which we referred to as the "file drawer problem". We did indeed argue that the available evidence suggested a lack of bias against the publication of null results; in fact, suggesting, if anything, a contrary bias against the publication of data showing a positive association. But Blettner *et al* dismiss our argument as "untenable," without justification.

However, evidence in support of our contention continues to accrue. For example, researchers (such as Melbye *et al* [6]) who are convinced of a null association continue to bolster their case by citing irrelevant data relating to spontaneous abortion. As we also clearly described in our review, spontaneous abortion is not associated with overall increased breast cancer risk, a finding consistent with well documented endocrinological differences between normal and spontaneously aborting pregnancies.

Further evidence of a lack of bias against publication of negative data is provided by the recent literature concerning oral contraceptive use and breast cancer, a literature which overlaps considerably with that concerning induced abortion and breast cancer. In designing their 1990 "review and meta-analysis" on oral contraceptives and breast cancer, Romieu *et al*[7] employed reasoning no different from our own, basing their study exclusively "on all available data" from published studies. They also argued against the existence of significant publication bias against null findings. They tested for a trend in relative risk versus study size, and concluded that, "There was no pattern, suggesting the absence of systematic bias in publication". (The lack of such a trend among the studies included in our own meta-analysis is also clear.) What better proof of the validity of this reasoning and this conclusion, than for the massive "collaborative reanalysis"[8] published last year in *The Lancet*, which included unpublished as well as published data, to arrive at the same overall result as had Romieu *et al*[7] (overall relative risk: 1.07 ± 0.017 versus 1.06 ± 0.08, respectively)?

The third criticism listed by Blettner *et al* relates to heterogeneity. That is, they fault us for performing "no investigation of heterogeneity". Indeed, we performed no quantitative test of heterogeneity among included studies, for lack of desire to prove the obvious, having duly noted that the included studies "differ widely in size and in many aspects of study design," but nonetheless display "a remarkably consistent, significant positive association between induced abortion and breast cancer incidence". We noted this consistency of a positive trend in our table 4, which showed that 16 of 21 studies (74%) reported an overall positive association, 10 with statistical significance. Here again, more recent reports have confirmed this trend, with 22 of 28 studies extant as of this writing reporting a positive association, 17 with statistical significance.

We also duly note the quantitative heterogeneity pointed out by Blettner *et al*, but disagree that this constitutes "a contraindication for estimating a pooled odds ratio". It may be argued, however, that a random effects model would have been more appropriate for arriving at a pooled odds ratio. We chose a fixed effects model in order to obtain the most conservative estimate of the pooled odds ratio (1.3; 95%CI 1.2, 1.4). A random effects model would be expected to yield an estimate closer to the unweighted average. We also calculated and presented the pooled, unweighted average (1.4; 95%CI 1.3, 1.6) which was in good agreement with the weighted average. We have now calculated the pooled weighted average of the 21 studies in the meta–analysis using a random effects model,[9] and it is the same as our initial result (1.3, 95%CI 1.1, 1.6), albeit with a wider confidence interval. Importantly, inclusion of all studies to date into this calculation (n = 28) yields the same result, the more recent data serving only to narrow the confidence interval (1.3, 95%CI 1.2, 1.5), thus confirming our initial result.

Yet Blettner *et al* carry the heterogeneity criticism even further, claiming: "The combination of crude (5 studies) and (logistic regression) model based odds ratios (16 studies) may yield biased results". One wonders how these critics overlooked our extensive discussion of just this point. In fact, we recalculated the weighted odds ratio and confidence interval, based on 15 of the 16 studies which used multivariate models, omitting the one[10] which did not account for age at first full term pregnancy. (This excluded study also happens to be one of the "positive outlying studies" in the radial plot prepared by Blettner *et al*) The weighted average thus obtained for these 15 studies did not differ significantly from the overall weighted average of all 21 studies, and it was still significantly positive (1.2; 95%CI 1.1, 1.3).

Finally, although it is our preference to focus solely on scientific issues, we believe it is appropriate to discuss the "politically and legally sensitive" nature of studies suggesting harmful effects of induced abortion, particularly in light of our critics taking such exception to our acknowledgement of that fact. Indeed, the tone of hostility in the suggestion of Blettner *et al* that the publication of our "so-called meta-analysis" was "unethical and harmful" is inescapable. Our study documented a literature in which the overwhelming majority of studies (16 of 21) had reported a positive association between induced abortion and breast cancer incidence, a fact even these harsh critics do not challenge. Blettner *et al* speak of the need of results such as ours to "be treated with caution". But caution in regard to what? Or to whom? Are they not aware that induced abortion is overwhelmingly an elective procedure? Would not caution in regard to proper patient care demand acknowledgement of the preponderance of available evidence that abortion is not only a risk factor, but the most *avoidable* of risk factors for breast cancer? Indeed, what perversion of standards of informed consent and patient care could place ethics and harmlessness on the side of *withholding* such knowledge from the very women who must live (or die) with the choices they make regarding abortion? That the criticisms raised by Blettner *et al* against our review and meta-analysis do not stand to reason is merely noteworthy, but the nature of the bias revealed in their critique (and in this they are far from unique) is deeply disturbing.

JOEL BRIND
Department of Natural Sciences, Baruch College, The City University of New York, New York, NY 10010 USA
VERNON M CHINCHILLI
WALTER B SEVERS
JOAN SUMMY-LONG
Center for Biostatics and Epidemiology and Department of Pharmacology, Pennsylvania State University College of Medicine Hershey, PA 17033 USA

1 Brind J, Chinchilli VM, Severs WB, Summy-Long J. Induced abortion as an independent risk factor for breast cancer: a comprehensive review and meta-analysis. *J Epidemiol Community Health* 1996;**50**:481–96.
2 Segi M, Fukushima I, Fujisaku S, *et al.* An epidemiological study on cancer in Japan. *GANN* 1957;**48**(Suppl):1–63.
3 Watanabe H, Hirayama T. Epidemiology and clinical aspects of breast cancer. *Nippon Rinsho* 1968;**26**:1853–9 (in Japanese).
4 Nishiyama F. The epidemiology of breast cancer in Tokushima prefecture. *Shikoku Ichi* 1982; **38**:333–43 (in Japanese).
5 Burany B. Gestational characteristics in women with breast cancer. *Jugosl Ginekol Opstet* 1979; **19**:237–47 (in Serbo-Croatian).
6 Melbye M, Wohlfahrt J, Olsen JH, *et al.* Induced abortion and the risk of breast cancer. *N Engl J Med* 1997;**336**:81–5.
7 Romieu I, Berlin JA, Colditz G. Oral contraceptives and breast cancer. Review and meta–analysis. *Cancer* 1990;**66**:2253–63.
8 Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormonal contraceptives: collaborative reanalysis of in-

dividual data on 53,297 women with breast cancer and 100,239 women without breast cancer from 54 epidemiological studies. *Lancet* 1996;347:1713–27.
9 Schmid JE, Koch GG, La Vange LM. An overview of statistical issues and methods of meta-analysis. *J Biopharm Stat* 1991;1:103–20.
10 Laing AE, Demenais FM, Williams R, Kissling G, Chen VW, Bonney GE. Breast cancer risk factors in African-American women: The Howard University Tumor Registry experience. *J Natl Med Assoc* 1993;85:931–9.

NOTICES

European Journal of Public Health – volume 7 (1) March 1997

Guest editorial
Citizens, users and health care *M Calnan*

Editorial note
Editorial note on journal development. *P-G Svensson, J Palm*

Original articles
Assessing the value of accreditation systems. *E Scrivens*
The relation between the number of symptoms and other health indicators in working men and women. *I Foppa, RH Noack*
Suicide reporting in Swiss print media: responsible or irresponsible? *C Frey, K Michel, L Valach*
Predictors of disability pension among young men: the role of alcohol and psychosocial factors. *M Upmark, T Hemmingsson, A Romelsjö, I Lundberg, P Allebeck*
Oral contraception and smoking: time trends for a risk behaviour in Finland. *EA-L Kosunen, AH Rimpelä, JA Kaprio, M-A Berg*
Appropriateness of hospital use: report from an Italian study. *G Apolone, G Fellin, A Tampieri, E Bonanoni, PF Crosti, E Lanzi, G Meregalli, G Trocino, A Liberati*
Dietary intake of some food items in smokers and non-smokers in a Mediterranean population. *M Martínez-González, R Pérez-Gutiérrez, J Martínez-González, M García-Martín, A Bueno-Cavanillas*
Income distribution and cause-specific mortality. *SJ McIsaac, RG Wilkinson*
Effects of primary health care reform on the prescription of antibiotics: a longitudinal study in a Spanish county. *S Juncosa, M Porta*
Hospital strategy reform in Romania: an experiment in Bucharest in 1993. *A-L Le Faou, A Marlier-Sutter, D Jolly*

Mammographic screening
Economic evaluation of a mammography-based breast cancer screening programme in Spain. *R Garuz, T Forcén, J Cabasés, F Antoñanzas, C Trinxet, J Rovira, F Antón*
How susceptible is the Antwerp female population to mammographic screening? *GF Van Hal, JJ Weyler, MM Matthyssen*

Perinatal and child health
Pre-natal care and prevention of low birth weight: a case-control study in southern Spain. *M Gómez-Olmedo, M Delgado-Rodríguez, A Bueno Cavanillas, A Herruzo Nalda, R Gálvez-Vargas*
Ethnic differences in rates of infant mortality and sudden infant death syndrome in Sweden, 1978 to 1990. *CEM Oldenburg, F Rasmussen, NU Cotten*
Childhood immunization: meeting targets yet respecting consent. *P Alderson, B Mayall, S Barker, J Henderson, B Pratten*

Short reports
A graphical display useful for meta-analysis. *FJ Jiménez, E Guallar, JM Martín-Moreno*
Association of waist to hip ratio with diabetes among middle-aged subjects with impaired glucose tolerance. *Q Qiao, S Keiänen-Kiukaanniemi, S-L Kivelä*
A population-based study of familial clustering of inflammatory bowel disease in Florence. *D Palli, C Saieva, G Trallori, G Bardazzi, G d'Albasio, M Milla, M Galli, O Tarantino, F Pacini*

Letter to the editor
News
Book reviews
Calendar of events
EUPHA section

Epidemiology—past and future. A joint meeting between the UK Society for Social Medicine and the *Journal of Epidemiology and Community Health* is to be held on Thursday, October 30, 1997 at the Weston Theatre, Manchester Conference Centre, UMIST from 10.00—16.30. Further details from Professor Charles Florey, Dept of Epidemiology and Community Health, Ninewells Hospitals and Medical School, Dundee DD1 9SY. Tel 01+382 632124. Fax 01+382 644197

Good Occupational Health Practice and Evaluation of Occupational Health Services, 8–10 June 1998, Hanasaari Cultural Centre, Espoo, Finland. Themes: good occupational health practice, evaluation, future perspectives. Deadline for abstracts: 31 January 1998. For further information: Ms Inkeri Haataja, Finnish Institute of Occupational Health, Topeliuksenkatu 41 aA, FIN-00250 Helsinki. Tel: +358 9 474 7470. Fax: +358 9 474 7548. email: Inkeri.Haataja@occuphealth.fi. http://www.occuphealth.fi/tiedotus/gohp.

BOOK REVIEWS

A simulation model for the future analysis of cardiovascular disease (with program diskette). O J Vriez, G M Boas, and J A H Janssen. A report commissioned by the Steering Committee on Future Health Scenarios (STG). (Pp 388; £45.00) Utrecht: International Books, 1995. ISBN 90-6224-878-0.
Health planning consists of formulating health goals and the means necessary for achieving these. Planning is thus a rational way of allocating resources so that the future can be steered in the most desirable direction. Setting objectives involves projecting foreseeable health scenarios, contrasting situations where healthcare intervention is absent and then where it is present. It is, therefore, extremely useful to have a software package capable of formulating future scenarios linked to the frequency of cardiovascular disease, and exploring the consequences thereof on the health of the general population, the public health system, and, in particular, the distribution of any related costs.
The software package, designed for DOS-based computers, comes complete with a user's manual which includes full information on the cardiovascular disease model used, development of the financial aspects, plus a wide ranging review of current knowledge on risk factors for cardiovascular disease and the efficacy of available preventive measures and methods of treatment.
The software is user friendly. Construction of scenarios and evaluation of the ensuing consequences requires data on: cardiovascular disease risk factor distribution in the target population; the expected effect of healthcare intervention on this distribution; cardiovascular disease incidence and fatality; and the natural history of the process in the absence of intervention. The fact that experts from the Mathematics, Health Economics, and Cardiology Departments at Limburg University collaborated on this project has ensured that both software and manual are marked by methodological rigour. In all three disciplines, book and diskette will prove a useful tool to those interested in health planning and a source of inspiration for the development of new products in this field.
Lastly, though software and manual are of universal interest, the fact that they are specifically based on the Dutch population and related cardiovascular risk factor distribution detracts somewhat from the program's utility vis-à-vis other populations. Furthermore, it would have lent greater insight, had the manual contained some information on the experience and impressions of Holland's Public Health Authority planners on using this software in the course of their routine work.

FERNANDO RODRÍGUEZ ARTALEJO
Professor of Preventive Medicine and Public Health, Universidad Autonoma de Madrid, Spain.

Management of neurological disorders. Edited by CM Wiles. (Pp 341; £24.95). London: BMJ Publishing Group, 1995. ISBN 0-7279-0903-7.
This book will either delight or slightly disappoint depending on the aims of the reader. It is a compilation of articles previously published in the *Journal of Neurology, Neurosurgery and Psychiatry* on the management of a wide variety of chronic neurological conditions, including meningitis. The book is well written, clear, and in general easy to read. It has useful summary boxes to highlight key points. The authors are all experts in their respective fields, and the chapters have fairly extensive references. Refreshingly, the authors have been encouraged to conclude their reviews with a section on auditing clinical care. This is done with less consistent success and perhaps reflects more the novelty of audit in neurology than any specific failings of the contributors. I was particularly pleased to see and enjoyed reading two chapters on "Resources and facilities" and "Neurorehabilitation", areas that are often neglected.
This book will be most useful for junior level hospital physicians, general practitioners, and medical students and is to be recommended. However, for public health physicians and purchasers it is of limited value or perhaps can be used as a first source of information. The sections on audit are on the "sketchy" side and the epidemiological content would make "needs assessment" difficult. Sur-