Induced abortion as an independent risk factor for breast cancer

Sir—In a recent paper Brind et al. 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 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—e.g., 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 neoplasms, 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 (1 and 2) 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.

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). 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) 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 example1, 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.

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Reply

We welcome substantive criticism of our "Comprehensive review and meta-analysis" 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 (df) 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., 1977?), 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. did not report the 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,5 and the other on a subsequent data base,14, and since these figures were in close agreement, we applied the means of the exposure rates from the other two to the Segi study. Then by 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 abortion occurred and the odds ratios calculated. We do not consider such elementary arithmetic “quite complicated”.

Yet still further along the “selection bias” track, 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, 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 reporting of a positive association. But Blettner et al dismiss our argument as “untenable”, without justification.

However, evidence in support of our contentions continues to accrue. For example, researchers (such as Melbye et al.) who are convinced of a null association continue to bolster their case by citing irrelevant data relating to spontaneous abortion and abortion history. Thus, by 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 abortion and spontaneous abortions complicating.

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 overall parallels 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. 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 results 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 to the validity of this reasoning and this conclusion, than for the massive “collaborative reanalysis” 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. (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 for heterogeneity in our 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 extent 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 “contradiction” and “an invalid 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 maintain the most favorable 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 as a random effects model, 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 continue their homogeneity 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 what, exactly, these critics fail to see. Our statistical discussion of just this point. In fact, we re- calculated the weighted odds ratio and confidence interval, based on 15 of the 16 studies which used multivariate models, omitting the one which did not account for age at first full term pregnancy (Tokoro, but the most also happens to be one of the “positive out- looking 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 average of all 21 studies, and it was still signifi- cantly 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 our publication of their so-called “meta-analysis” was “unethical and harmful” is inescapable. Our study docu- mented a literature in which the over- whelming majority of studies (16 of 21) had reported a positive association between induced abortion and breast cancer incidence, a fact essentially ignored by Blettner et al. Blettner et al speak of the need for 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 a medical practice and therefore 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 with- holding or withdrawing a medical procedure from 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.
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BOOK REVIEWS

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 feasible 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 mortality; and the natural history of disease. It is, therefore, 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 software than any specific failings of the contributors. I was particularly pleased to see and enjoyed reading the first 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-