Induced Abortion as an Independent Risk Factor for Breast Cancer: A Systematic Review and Meta-analysis of Studies on South Asian Women

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ABSTRACT:
Objective: South Asia, a historically low-incidence region for breast cancer, has produced many recent studies examining reproductive factors. We compiled these studies to confirm the reality of the significant association reported in the first, 1996 review of induced abortion as a risk factor, independent of abortion's known effect in abrogating the protection afforded by full-term pregnancy.
Methods: We searched the medical literature for English language studies on breast cancer incidence in women in South Asia published from 1 January, 2000 through 30 June, 2017, using Pubmed, Scholar-Google, and bibliographic searches. Studies were included which reported overall data on induced abortion and/or abortion non-specifically. All 20 eligible studies were of retrospective, case-control design. Data from individual studies were combined using random effects modeling, following the determination of significant heterogeneity.

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Results: **Cumulative OR for all 20 studies was 2.51 (95%CI: 1.67–3.75) and 3.91 (95%CI: 1.02–14.97) for the five studies which reported specific data on induced abortion. Significant dose-dependence was observed among all 5 studies which stratified by number of abortions. Meta-regression of OR v. abortion prevalence among controls was statistically significant, as observed in a 2013 meta-analysis in China.**
Conclusion: **The moderately strong association identified between abortion and breast cancer explains in part the spread of the breast cancer epidemic to South Asia as it has become Westernized. Continuing denial of the abortion-breast cancer association can only ensure that the acknowledged worldwide breast cancer epidemic will continue to worsen, costing many millions of women their lives over the next several decades.**

An earlier "comprehensive review and meta-analysis" coauthored by one of us (JB)[1] on the association between induced abortion and breast cancer, stated that the extant worldwide literature had already demonstrated "a remarkably consistent, significant positive association between induced abortion and breast cancer incidence, independent of the effect an induced abortion has in delaying first full term pregnancy (FFTP)." Moreover, the authors observed that the biological knowledge at the time reflected "a plausible and likely mechanism by which the surging oestradiol of the first trimester of any normal pregnancy, if it is aborted, may add significantly to a woman's breast cancer risk."[1] Importantly, if these conclusions were correct, the impact on breast cancer incidence should be clearly evident by now, over 20 years later. This is especially true considering the worldwide expansion of legalized abortion during the late 20th century and the latency in the development of breast cancer. In fact, evidence abounds that supports this conclusion, especially as elective abortion has played its part in the "Westernization" of cultures in the developing world, such as in Asia. In regard to mainland China, for example, Linos et al.[2] stated unequivocally in 2008: "China is on the cusp of a breast cancer epidemic." By 2013, Huang et al.[3] had amassed 36 primary studies in China in their systematic review and meta-analysis (SRMA). They reported a statistically significant 44% increase in breast cancer incidence associated with induced abortion, which risk increase rose with the number of abortions (76% for two or more abortions and 89% for three or more abortions) among Chinese women.

Clear and abundant evidence notwithstanding, the reality of the abortion-breast cancer association is still widely discounted or disputed. For example, Linos et al.,[2] in their lengthy analysis of "an emerging epidemic of breast cancer in China," managed to avoid a single mention of the word abortion, even as they predicted that millions of Chinese women would fall victim to breast cancer in the coming decades, "where breast cancer incidence rates are approaching those in Western nations, in which breast cancer is the most commonly diagnosed female cancer."[2]

In addition to the dozens of studies emerging from China, many studies reporting on reproductive risk factors for breast cancer have also been published in South Asia in recent years. However, these have largely appeared in obscure journals, and have attracted little interest in the West. It is therefore our aim to systematically review the South Asian studies to confirm the predictions made over 20 years ago on the basis of earlier studies. Moreover, since much of the resistance to these findings was based on the relatively weak associations reported in earlier, worldwide studies, the low prevalence of other risk factors (e.g., nullliparity, late age at FFTP, lack of breastfeeding, alcohol consumption) among South Asian women should provide a better study population for any real association with induced abortion to emerge clearly.

Materials and Methods

Search Methods

The medical literature was searched for studies on breast cancer incidence in women in South Asia (India, Pakistan, Bangladesh, Sri Lanka, Bhutan, and Nepal) published in the English language during the period 1 January, 2000 through 15 March, 2017, using search engines Pubmed and Scholar-Google, with the following keywords: abortion, abortions, "induced abortion," "pregnancy losses," "termination of pregnancy," "history of abortion," "abortion history," "bad obstetric," parity, "number of abortions," "breast cancer," "breast carcinoma," "carcinoma breast," "risk factors for breast cancer," India, Pakistan, Sri Lanka, Bangladesh, Bhutan, Nepal.

Bibliographies of all studies identified were also searched. In all, 26 primary studies were located.

Eligibility Criteria and Study Selection

All studies that reported overall effect size incidence data as odds ratios or relative risks and 95% confidence intervals (95% CI) were included, if breast cancer cases were compared to an unaffected control group, whether adjusted for confounders or not. Studies were also included if the raw data provided permitted overall ORs to be calculated. Although the exposure variable of interest was induced abortion, all studies were included whether induced abortion data were reported specifically, or simply "abortion" was reported. The exclusion from the 1996 meta-analysis[1] of studies not reporting specifically on induced abortion, was on the basis of most abortions reported at that time being spontaneous abortions (miscarriages). However a much higher proportion of abortions reported in recent years are induced, and most South Asian studies do not distinguish between induced and spontaneous abortion. Moreover, since it is well established that spontaneous abortions do not increase breast cancer risk,[4] it is clear that the relative risk of breast cancer attributable to abortion nonspecifically will provide an underestimate of the relative risk attributable to induced abortion, thus underscoring the importance of a positive association.

One Indian case-control study[5] was excluded because, although it examined reproductive risk factors for breast cancer, the word "abortion" was never mentioned at all; one study[6] was excluded because of missing data, i.e., no abortion data on nulliparous women, and because of discrepancy between the null adjusted OR (0.98; 95% CI 0.61 – 1.56) and the positive association represented by the text. One study[7] was excluded because it reported only on abortions before first full-term pregnancy (FFTP), rather than abortions overall; one study[8] was excluded because it reported an OR of 1.320 for "history of abortion," but with no 95% CIs nor raw data reported; and two studies[9,10] were excluded for lack of a non-cancer control group. Hence, the overall meta-analysis was performed on a total of 20 primary studies: 16 from India,[11-26] 2 from Bangladesh,[27,28] and one each from Pakistan[29] and Sri Lanka.[30] All included studies embodied a retrospective case-control design.

Data Extraction and Analysis

All studies were reviewed to determine if they could provide odds ratio (OR) effect size data. For studies which did not report ORs, we reconstructed the ORs from raw data provided. Where provided (5 studies), specific data for induced abortion were used. Where only data on unspecified abortion were provided, these data were used as the measure of induced abortion.

Since only five studies reported abortion data adjusted for confounding variables in addition to unadjusted data,[19,20,26,28,30] the unadjusted dataset was used to calculate the overall OR for abortion among all studies (Fig. 1). We also combined the adjusted datasets in a separate analysis.

Since the study populations differed substantially from study to study (e.g., differing proportions of urban and rural subjects), we used the random effects model for the meta-analysis. The random effects model assumes that the various studies which are meta-analyzed represent a random sample of studies which represent the true effect,[31,32] We employed the statistical package "Comprehensive Meta-Analysis" (Version 2) by Biostat (Englewood Cliffs, NJ, USA).

Results

Table 1 lists the population characteristics of included studies, and illustrates the tremendous variation in study design. While most of the studies were similar in size, the population size ranges from as few as 20 patients to 1637. The geographical source of subjects also reflects locales from all over South Asia. Most of the patients were drawn from hospitals, however some studies were of inpatients; some outpatients, and some not clearly specified. Moreover, controls were selected in a variety of different ways; some selecting from among inpatients with non-cancer diagnoses and some from among non-hospitalized healthy women. In terms of effect size data, all studies reported raw data and crude ORs and/or multivariate adjusted ORs. Only five studies reported multivariate adjusted ORs,[19,20,26,28,30] another group of five studies reported data specific

Table I. Population Characteristics of Included Studies

1st Author	Year of publication	Year(s) of study	No. patients/ controls	Nation & locale	Data type	Strat by No. Ab?	Specific IA data?
Samson[11]	2007	not shown	250/500	South India	raw	-	-
Rai[12]	2008	2006-07	65/65	Varanasi, India	U*	-	-
Pakseresht[13]	2009	2006	115/217	New Delhi, India	U	-	-
De Silva[30]	2010	2007	100/203	Western Sri Lanka	U,A**	-	-
Kaur[14]	2011	2003-05	115/123	India (non-specific)	U	+	-
Lodha[15]	2011	2008-09	215/215	Bhopal, India	U	-	+
Raza[29]	2011	not shown	224/224	Karachi, Pakistan	raw	-	-
Langer[16]	2012	2004-05	100/100	Jammu, India	U	+	-
Santhy[17]	2012	2008-2010	200/200	Coimbatore, India	U	+	-
Balasubramaniam[18]	2013	2004-05	152/152	Pondicherry, India	U	-	-
Bhadoria[19]	2013	not shown	320/320	New Delhi, India	U,A	-	-
Jabeen[27]	2013	2009-10	262/262	Dhaka, Bangladesh	U	-	+
Kamath[20]	2013	not shown	94/94	Manipal, India	U,A	-	+
Parameshwari[21]	2013	2012	20/80	Kerala, India	raw	-	-
Roy[22]	2014	2010-11	108/128	Kolkata, India	raw	-	-
Takalkar[23]	2014	2009-13	220/220	Maharashtra, India	U	-	-
Babita[24]	2014	2009-10	128/128	Haryana, India	U	-	-
Ahmed[28]	2015	2011-14	80/80	Bangladesh	A	-	+
Mohite[25]	2015	2009-11	217/217	Maharashtra, India	U	+	-
Nagrani[26]	2016	2009-13	1637/1515	Mumbai, India	A	+	+

*Unadjusted ORs reported **Adjusted ORs reported

Figure 1. Full data set: All abortions, unadjusted ORs, random effects model

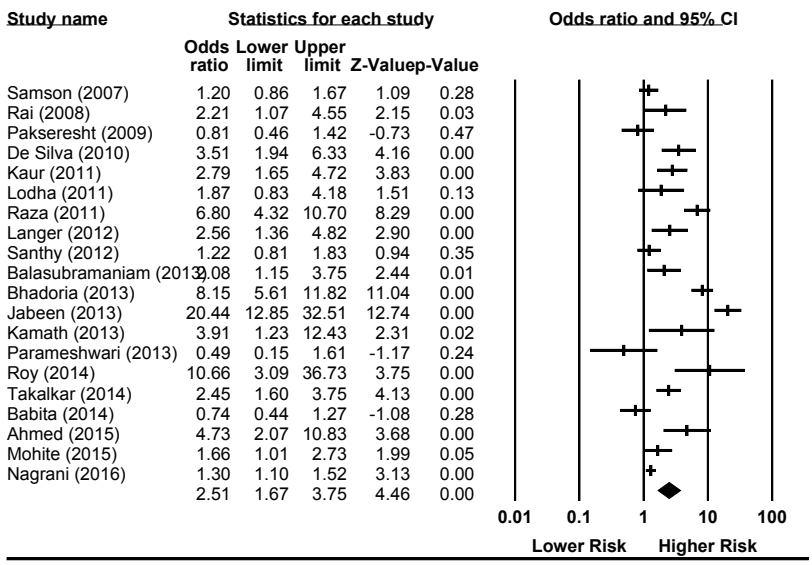


Figure 2. Induced abortion, unadjusted ORs, random effects model

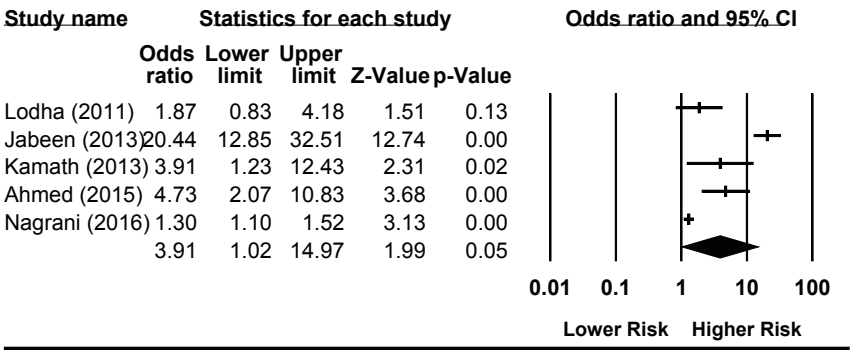
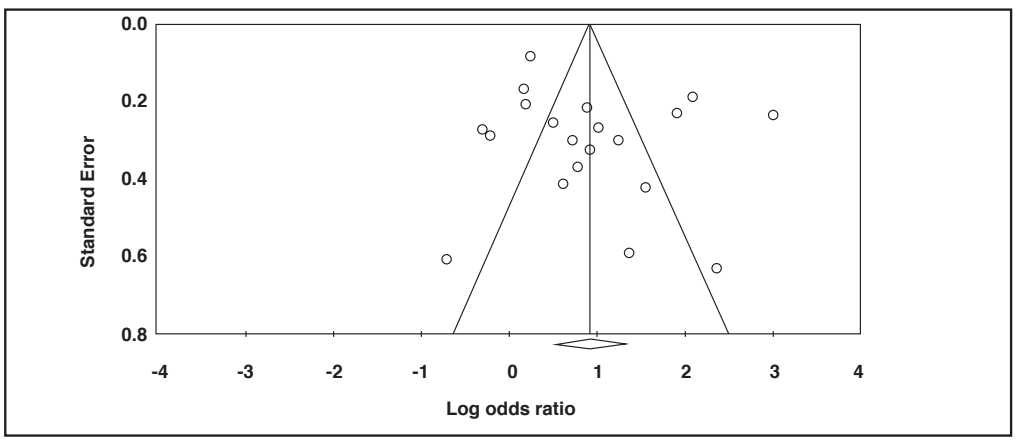


Figure 3
Funnel plot of standard error by Log OR, full data set, unadjusted ORs



Q = 269 (p < 0.0001); I^2 = 92.9; τ^2 = .0739

to induced abortion (rather than simply "abortion"),[15,20,26-28] and another group of five studies stratified ORs by number of abortions.[14,16,17,25,26]

The summary of overall ORs (i.e., for one or more abortion), using unadjusted ORs, appears in Fig. 1. When the data for the five studies that reported multivariate adjusted ORs is replaced by the adjusted data (Fig. 2), the significant overall OR (2.51; 95% CI 1.67 – 3.75) is not substantially changed (OR 2.37; 95% CI 1.62 – 3.48). Among the five studies which reported data specific to induced abortion, the overall OR was substantially higher (OR 3.91; 95% CI 1.02 – 14.97) and still statistically significant (Fig. 2). The substantial and significant heterogeneity of the 20 included studies is reflected in the funnel plot (Fig. 3). The clear and significant dose dependency of the abortion-breast cancer association is shown in Fig. 4, in which all 5 studies which stratified data by number of abortions show the same trend of increasing risk with increasing number of

Figure 4
Dose-dependence of abortion-breast cancer association

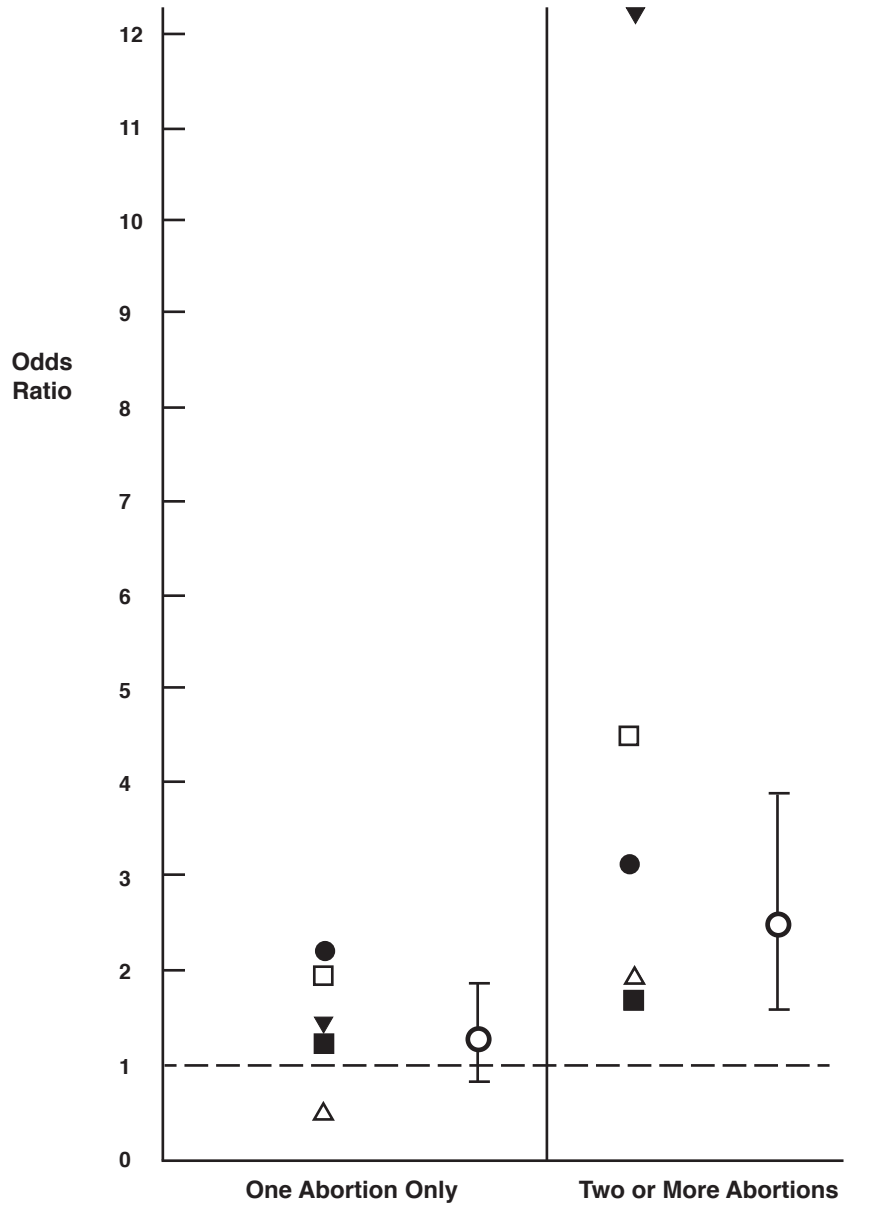
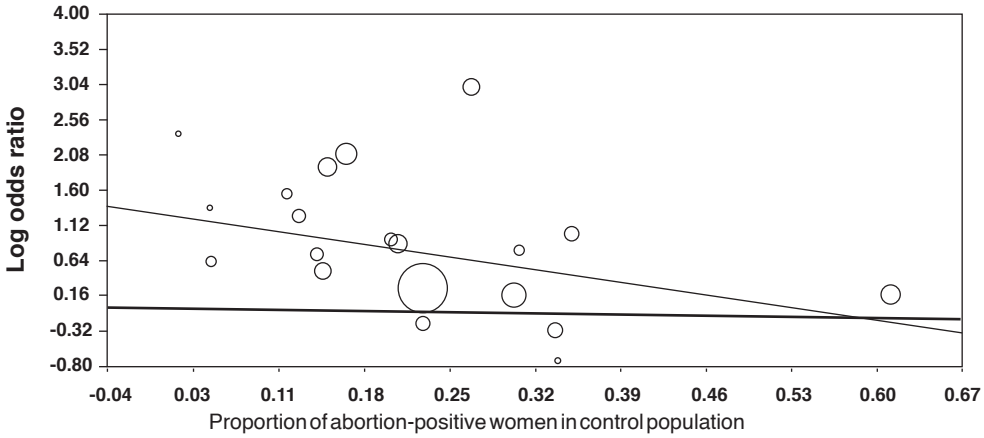


Figure 5
Meta-regression of prevalence of abortion in the control group with logOR



Each circle represents an individual study, with area inversely proportional to variance. Slope of regression line: -2.375 (95%CI: -3.245, -1.505; p<0.0001) y-intercept: 1.288 (95% CI: 1.056, 1.520; p<0.0001). x-intercept (logOR=0): 0.60

abortions. Fig. 5 shows the clear and significant trend of decreasing OR with increasing prevalence of abortion in the control population (taken as representing the general population). Above an abortion prevalence of approximately 59% of the control population, a negative overall abortion-breast cancer association is to be expected.

Discussion

"Abortion" v. "Induced abortion" as Exposure Variable

Most South Asian studies do not distinguish between induced and spontaneous abortion, rather reporting on exposure to abortion non-specifically. Only three studies[15,20,26] reported specific data for induced abortion and spontaneous abortion, whereas the two studies on women from Bangladesh[27,28] reported data on induced abortion only. Therefore, we attempted to use the relative proportions of induced and spontaneous abortion-exposed control subjects to estimate how many of those with unspecified abortion could be considered to have had induced abortions, among all studies. Subjects in the small pair-matched study by Lodha et al.[15] were matched for locale, and the prevalence of abortion among controls was 4.8 induced and 3.8 spontaneous (i.e., 10 out of 18, or 55.6% of abortions were induced). Kamath et al.[20] included 94 patients and 94 controls from both urban and rural areas (although how many subjects from each was not reported.) The prevalence of abortion among controls was 4.3% induced and 13.8% spontaneous. Hence, 4 of 17 subjects, or 23.5% of subjects with any abortions had induced abortions. In Nagrani 2016, the prevalence of (one or more) induced abortion was 26.0% among urban controls, and 16.6% among rural controls. In contrast, the prevalence of spontaneous abortion showed less urban v. rural difference, i.e., 18.2% among urban controls and 21.7% among rural controls. The much higher prevalence of

induced abortion among urban controls thus results in 58.8% of total urban abortions being induced, and only 43.3% of total rural abortions being induced.

The weighted average proportion of subjects with induced abortion among total subjects in these three studies with any abortion was therefore 357/673 = 53.0%. Huang et al.[4] in their meta-analysis of 36 primary studies from China, found an aggregate OR for induced abortion of 1.49 (95% CI 1.23 – 1.74) when they combined (14) studies which reported data specifically on induced abortion, and 1.44 (95% CI 1.29 – 1.59) when they included all studies, whether or not induced abortion was separately reported. They also cited other published reports which provided a reliable estimate that over 90% of all abortions in China are induced. Hence, the underestimation of aggregate OR for induced abortion using all studies was small. In the present analysis, the underestimate of aggregate OR for induced abortion is clearly more substantial, owing to the lower overall incidence of induced abortion among women in South Asia compared to women in China.

Strength of Association and Dose Effect: Evidence for Causal Inference

The 1996 review[1] of worldwide abortion-breast cancer data concluded that "a broad base of statistical agreement" coupled with "a plausible and likely mechanism" justified the inference that induced abortion is causally related to breast cancer incidence. This conclusion came under wide criticism, based on the fact that the overall observed association was weak (OR = 1.3), and the lack of demonstration of a dose effect. The moderately strong overall association in the present analysis (OR = 2.51) argues substantially in favor of a causal explanation. Moreover, the significant overall dose effect (Fig. 4) resulting from the meta-analysis of the five South Asian studies that stratified abortion exposure by one versus more than one abortion,[14,16,17,25,26] lends further weight to a causal inference.

Urban v. Rural Differences

The differences in both lifestyle (including prevalence of induced abortion) and breast cancer incidence between urban and rural women in South Asia are substantial[26] and might also explain some of the heterogeneity observed among studies, as shown in the funnel plot (Fig. 3). Among the included studies, only Nagrani et al.[26] analyzed urban and rural populations separately. In their study, the incidence of induced abortion among the 972 urban controls was 26.0%, but only 16.6% among rural controls. Among the other 19 included studies, the study population of Roy et al.[22] was all urban, those of Balasubramanian et al.[18] and Mohite et al.[25] were mostly or entirely rural, and those of Lodha et al.,[15] Langer et al.,[16] and Parameshwami et al.[21] were matched for residence. Ten of the studies[11,12,14,17,19,20,23,28-30] made no observations of urban versus rural differences among cases and/or controls. These presumably included substantial numbers of both urban and rural subjects, although only Kamath et al.[20] explicity reported this. Babita et al.[22] reported a small difference between cases (56.3% rural) controls (63.3%) rural, but two studies reported large and significant difference between cases and controls.

Specifically, Pakseresht et al.[13] reported 43.5% rural cases and only 30.9% rural controls, whereas Jabeen et al.[27] reported essentially the opposite, i.e., that 71% of the cases were urban, although only 34% of the total study population was urban. Therefore, with the incidence of induced abortion generally higher among urban compared to rural women, the disproportionately higher number of urban controls in the Pakseresht study[13] would be expected to drive down the overall OR, and the disproportionately lower number of urban controls in the Jabeen study[27] would drive up the overall OR. Accordingly, these two studies are outliers in the expected opposite directions re: the overall OR, Pakseresht et al. reporting OR = 0.81 and Jabeen reporting OR = 20.44 (Fig. 1).

Reporting or Response Bias: Under-reporting by Controls v. Cases

The main argument put forth to explain away the positive association observed in 1996 meta-analysis,[1] based on the weakness of the association and the lack of a dose effect, was reporting or response bias. The hypothesis: "A woman with cancer is perhaps more likely to remember and report a previous abortion than a healthy control," was first raised in 1989 by Harris et al.[33] Since theirs was a study based on prospective, Swedish registry data, the authors suggested that the positive associations reported in most previous papers could have falsely resulted from reporting bias (also called response bias or recall bias). In a subsequent paper,[34] these authors claimed to present significant evidence of response bias, by comparing their Swedish registry data to interview-based data on the same Swedish women. They reported a statistically significant difference "($p < 0.007$) between underreporting of previous induced abortions among controls relative to overreporting among cases." Since that time, response bias has been widely invoked to minimize or explain away all findings of positive associations between induced abortion and breast cancer. This is most curious, considering the utter dependence of the Lindefors-Harris evidence upon the dubious notion of "overreporting," i.e., the idea that breast cancer patients would report abortions that had never taken place. After enduring severe criticism,[35,36] the "overreporting" notion was ultimately retracted by its proponents, who admitted, "We are not surprised to find some Swedish women confidentially reporting having had induced abortions during the period 1966-1974 that are not recorded as legally induced abortions."[37]

Nevertheless, the reporting bias hypothesis has continued to be reported almost as established fact. Thus, for example, a high-profile "collaborative reanalysis" of worldwide abortion-breast cancer data[3] concluded: "Systematic differences in the reporting of known past induced abortions between women with and without breast cancer in case-control studies could well produce a falsely positive association between the risk of breast cancer and a retrospectively reported history of induced abortion" (Beral 2005), based on the dubious data of Lindefors-Harris et al.[34] despite the fact that no real evidence of actual reporting bias in the direction of overestimating relative risk has ever been reported. Even the most recent South Asian study[26] echoes the presumption of validity of reporting bias as a justification for presuming that the positive abortion-breast cancer association is an artifact: "However, most previous case-control studies have observed a positive associ-

ation between induced abortion and breast cancer, whereas most cohort studies have not, suggesting that the increased risk observed in our and other case-control studies is likely to be due to recall bias." This, despite the fact that these last authors' own study clearly evidence a dose-effect in both urban and rural Indian women.[26]

Retrospective v. Prospective Data: Elimination of Possible Reporting Bias

The response bias-based dismissal of the reality of the positive abortion-breast cancer association has been supported by the publication of several large studies based on prospective data.[38-46] It is unarguable that a study based on prospective data is not subject to reporting bias, since ascertainment of exposure status (abortion) necessarily antedates that of disease outcome (breast cancer). Hence, it is argued that studies based on prospective data are superior to retrospective-data-based studies (typical case-control studies), but this is only true if the studies are equally sound otherwise.

By far the largest and most widely cited prospective data-based study on induced abortion and breast cancer is the 1997 cohort study by Melbye et al.[38] on women in Denmark. Since the Melbye study was based on medical records of abortion on 1.5 million Danish women, among whom were performed over 370,000 abortions and were diagnosed over 10,000 cases of breast cancer, their reported overall statistic of relative risk of 1.00; 95% CI: 0.94 – 1.06 has been widely touted as virtual proof of a null association. Several smaller European and US studies also subsequently reported similar results between 1997 and 2008,[39-46] bolstering this claim. All of these studies, however, have come under serious criticism for a host or methodological defects, including frank violations of the scientific method.[4,47-58] For example, the study of Melbye[38] had misclassified over 60,000 who had had one or more induced abortions, as not having had any abortions, their records having been inexplicably excluded from the available records of abortion exposure. This massive misclassification alone renders invalid the summary overall statistic of a null association and its very tight 95% confidence interval. Moreover, the ascertainment period for both exposure and outcome ended on the very same date, thus allowing for as little as zero follow-up time for the exposure to produce the putative outcome; plainly an absurdity. Adding to the absurdity is the fact that over one fourth of the cohort (i.e., 358,000 women) were actually under the age of 25 at the termination date of the study; which allowed the inclusion of tens of thousands of abortions among a portion of the population among whom were diagnosed fewer than 10 cases of breast cancer. Yet the most obvious violation of the scientific method by Melbye et al.[38] was the use of an exposure (induced abortion) database that began in 1973, linked to the outcome (breast cancer) database that began in 1968, as if outcome could precede exposure!

Reporting Bias: Under-reporting by Cases v. Controls

Nevertheless, such seriously flawed studies are to this day cited as proof of a null association. In the present review, which is comprised exclusively of retrospective, case-control studies, the strength and dose dependence of the overall association argue

against response bias as an explanation for the positive association between abortion and breast cancer. However, it cannot necessarily be dismissed as having no effect upon the result. In fact, some evidence does appear in several of the South Asian reports, as well as in at least one earlier report in the US, of underreporting by cases—not controls. Such evidence would cause an underestimation—rather than an overestimation of the association.

In the 2004 (excluded) study of Pakistani women by Gilani and Kamal,[6] each hospital patient was compared to one urban and one rural population-based control subject. In order "to reduce the effect of interviewer bias," all cases and controls were interviewed by the same interviewer. Nevertheless, there is a striking discordance between cases and controls in the number of subjects for which abortion data are missing. In fact, all the dichotomous reproductive variables show far more missing data among cases than controls, with the discordance widest for abortion (93 out of 392 cases, or 23.7%, and only 1 out of 928 controls). The crude OR for abortion in this study is 1.72, with the missing data excluded, and it would rise to 3.22, were all the cases of missing data to represent a positive history of abortion. This seems a plausible hypothesis, since, as the authors note: "Induced abortions are not supported by Pakistani society, so to avoid any mis-reporting, participants were not asked to specify the type of abortion." But why is there such a tremendous bias between cases and controls? We propose here a simple answer: One might expect that hospital patients would be more likely to agree to be interviewed for a study, perhaps feeling that refusal to participate might negatively impact their treatment (Interestingly, the rate of refusal to participate is not reported.) Once recruited, patients might then decline to report on the stigmatizing exposure of abortion (and other reproductive variables as well). But controls, recruited randomly from the population, might be more likely to decline to participate in the study altogether if they were uncomfortable about disclosing such personal information (and here again, the rate of refusal was not reported. Potential control subjects were solicited until the required quota for the study was achieved.) Hence, it is not surprising that at least 97% of controls provided information about all reproductive variables; 99.9% providing abortion history. We have excluded this study from the present review due to the discrepancy between the null result reported in the data table (adjusted OR 0.98; 95%CI 0.61 – 1.56) and the statement in the text that "a history of abortions" was among "the characteristics found to increase risk" in their multiple logistic regression model, as well as the fact that they limited their data on abortion to parous women only.) However, a similar bias appears in the data of Lodha[15] wherein abortion data were missing from 13 out of 215 (6.0%) cases, v. only 6 out of 215 (2.8%) controls. Lodha et al. reported raw data that calculates to a crude OR of 1.87 (95% CI 0.83 – 4.18; Corrected data provided by authors via personal correspondence). Although Lodha et al. did not report the MLR-adjusted OR for induced abortion since it did not achieve statistical significance, the OR may have been artificially low due to reporting bias.

Among five other of the included South Asian studies, a similar situation is suggested by the description of case selection. Specifically, these[13,16,18,21,24] included all patients diagnosed within a given time period, and either stated or implied 100% case participation, even though they reported that informed consent was obtained. Here again, if breast cancer patients felt that opting out might negatively impact their treatment, they might have agreed to participate, while under-reporting on sensitive issues such as abortion. Controls, on the other hand, likely refused at some rate (not reported), being easy to replace with other volunteers. It is noteworthy that among these five studies are all three which reported ORs <1[13,21,24] thus supporting the suggestion that selection bias and the resulting reporting bias may have affected the result in the direction of underestimation of the OR.

A similar likelihood of subtle reporting bias has also appeared in a US study. Specifically, in their 2003 population-based study, Mahue-Giangreco et al.[59] reported a rather high "patient refusal" (to participate) rate of 11.5% of eligible patients, in a fixed pool of 969 eligible patients, interviewed at home. Controls, on the other hand, were recruited via a "neighborhood walk" protocol. Any eligible controls who refused to participate were simply replaced by recruiting others from the neighborhood. It seems reasonable to suggest that women who are reluctant to disclose a history of induced abortion would be more likely to opt out of a study in the first place (unless there is some subtle coercion at work), rather than agree to provide sensitive information (by agreeing to participate in the study) and then withhold it. Therefore, if abortion-positive patients were substantially over-represented in the large group of patients refusing to participate, the OR might be substantially underestimated due to the resulting selection bias. Hence the reported overall OR (0.69; 95% CI 0.46 – 1.04) may well have been underestimated as a result.[59]

Other Sources of Bias and Confounding

The largest, most recent and ostensibly most well designed of the included studies is that of Nagrani et al.[26] As this study is about an order of magnitude larger than most of the other studies, it has the most weight in the overall meta-analysis. Moreover, it is the only study that reported on induced abortion specifically and adjusted the ORs for a number of potential confounders and stratified by number of abortions. It is therefore noteworthy that Nagrani et al. also reported the lowest overall OR for induced abortion (OR 1.30; 95% CI 1.11 – 1.53, pooled from the separate ORs they reported for urban and rural populations). Yet there are several aspects of the Nagrani paper which are very unusual and may serve to explain its somewhat discordant results in terms of bias and/or confounding.

The selection of patients from Tata Memorial Hospital in Mumbai in Nagrani et al. appears straightforward, but there is no direct indication as to how many of the patients and controls were nulliparous. Instead, parity is reported in 4 strata of "No. of full-term pregnancies": 1 (reference stratum), 2, 3 and 4 or more. This is odd, since all other included studies included nulliparous women in their calculations of the effect of parity.

Hence, it was necessary to calculate the number of nulliparous women in the Nagrani study indirectly, by subtracting the numbers of urban and rural patients and controls reported as having had any full-term pregnancies, from the numbers of urban and rural patients and controls in the total population (which is the same as the total numbers reported as having 0, 1 or 2 or more induced abortions.) Accordingly, we calculate that 98/1195 (8.2%) urban patients and 77/972 (7.9%) urban controls were nulliparous, and that 8/442 (1.8%) rural patients and 16/543 (2.9%) of rural controls were nulliparous. These data are quite striking, in two ways. First, there is a more than three-fold difference in the nulliparity rate between urban and rural subjects (approximately 8% urban v. approximately 2.5% rural). Secondly, there is no significant association between nulliparity and breast cancer, whereas the observation of a positive association is well established and practically universal,[35] among South Asian studies as well. If anything, nulliparity appears somewhat protective in the Nagrani et al. study, especially among rural women (although the number of nulliparous rural women is very small). It is possible that the unusual results re: nulliparity are related to the unusual way in which the controls were selected.

Controls were selected from among cancer-free "female visitors…who were accompanying cancer patients." No doubt many of these visitors were related to the patients they accompanied, and this could be expected to affect the results of various comparisons. For example, even though family history of breast cancer is well established as a risk factor for breast cancer, family history shows up in the Nagrani study as a protective factor. Among urban women especially, twice as many controls (8.3%) as cases (4.1%) reported a positive family history of breast, endometrial or ovarian cancer. This is almost certainly a result of the control selection process, considering that every control subject who is related to a study patient has a positive family history of breast cancer, by definition. Yet the authors make no mention in the text of family history at all, let alone of this anomaly that shows up in the data table.

Yet stranger still, controls "were frequency matched to cases based on age (+/- 10 years)." Such a large age range as a matching window is unheard of in studying any disease with a steep age-incidence curve as is breast cancer.[60] Hence, the significant difference ($p = 0.007$ for urban and rural subjects combined, by t-test) in the (younger) age profile of controls compared to patients, serves to lower the observed association with induced abortion. Moreover it is troubling that Nagrani et al. also failed to note at all this significant difference in age between cases and controls, as would be customarily reported in the first table.

Nagrani et al.[26] also devote substantial discussion to the significant negative, dose-dependent association they observed with spontaneous abortion. But strangely, they hypothesize that the "it is plausible that the observed protection may reflect the protection acquired by pregnancy." However, the protective effect is known to apply only for pregnancies that last at least 32 weeks.[61] Moreover, since the number of spontaneous abortions tends to parallel the number of full-term pregnancies, and since full-term

pregnancies are also protective, the observed protective effect of spontaneous abortion may result from confounding by full-term pregnancies, which their multivariate model did not account for (They adjusted for age at FFTP instead).

Finally, it is troubling that Nagrani et al. conclude "that the increased risk observed in our and other case-control studies is likely due to recall bias," merely on the basis of their study's being retrospective in design. This despite the clear dose-dependence of their own reported significantly positive association and the existence of so many positive South Asian studies, not one of which was cited. This is troubling because it reflects an ***a priori*** rejection of any real risk-increasing effect of induced abortion, a position with no scientific validity.

Meta-Regression Analysis and the Prevalence Problem

In addition to the reporting/response bias argument against the positive association emerging from retrospective data-based studies, data emerging from several studies in Shanghai, China, both retrospective[62,63] and prospective,[41] have also shown a null association between induced abortion and breast cancer. The consistency of this finding and the very large populations under study have been used to bolster the reporting bias argument.[41,63] Moreover, Ye et al.[41] argued against response bias among the Chinese study population, in which they claimed that, due to its long-standing legality and wide acceptability, "under-reporting of most induced abortions would not likely be an important problem."[41] As Brind and Chinchilli argued in response to Ye et al.[53]:

> Once the prevalence of a given exposure rises to a level of predominance, it is prudent to ask whether indeed the unexposed comparison group has instead become a subgroup, which is unexposed for some reason that bears relevance to its risk profile for the disease in question. In such a case, statistical adjustment cannot remove all such confounding, since the calculation of the adjustment term will necessarily be underestimated.

In terms of breast cancer, those with no abortions are more likely those who are less fertile, and/or have their first full-term pregnancy (FFTP) at a later age, thus constituting a sub-group at higher risk than the general population. According to Huang et al.[3] this hypothesis "was well exemplified by the meta-regression analysis in our study." In their meta-regression curve the meta-regression line crosses the line OR = 1 at approximately 69% prevalence of induced abortion among controls. Hence, the observed OR of earlier Shangai studies[41,62] wherein the observed prevalence of induced abortion among controls was 66% and 51%, respectively, was not significantly different from 1.0.

A subsequent study on Shanghai women essentially confirmed the prevalence problem with studies where abortion prevalence is especially high. Specifically, Wu et al.[63] reported a null result (OR=0.94; 95%CI= 0.79-1.11), and, despite the prevalence of induced abortion being 70.5% among controls, concluded "that a history of induced abortions may not increase the risk of breast cancer." But the disappearance of a positive association—and even the appearance of a negative association—between abortion and breast cancer in studies where abortion prevalence is particularly high has also shown

up in some European studies. Thus in a 1979 study in Yugoslavia[64] wherein the induced abortion prevalence among controls was 75.2%, and a more recent study in Serbia (formerly part of Yugoslavia),[65] wherein the prevalence was 80.1%, the reported ORs for induced abortion were 0.50 (95% CI 0.33, 0.74), and 0.47 (95% CI, 0.25-0.90), respectively. For these studies, the prevalence is so high that the present meta-regression graph (Fig. 5) would have to be extended, and the point estimates for log OR would fall well into the range of negative association, along the regression line. But rather than indicating a true null or negative association, such results demonstrate that populations in which the majority of women have had at least one induced abortion, are unsuitable for studying abortion as a risk factor for breast cancer.

In contrast, South Asia, where the prevalence of induced abortion is still relatively low (and much lower in rural, compared to urban women), provides an eminently suitable population for the study of this putative association.

Biological Basis of the Abortion-Breast Cancer Link

That the development of breast cancer is related to pregnancy is unarguable, and the possibility of a biological basis for a risk-increasing effect of induced abortion has never been disputed. In fact, the risk-increasing effect of delaying FFTP or reducing parity by any means, including induced abortion, has long been recognized.[66,67] This effect is attributable to the fact that full-term pregnancy (FTP)—especially a woman's first—lowers risk by promoting the differentiation of 70 - 90% of the breast lobules[68,69] and reducing the number of stem cells therein,[70] thus rendering them permanently resistant to malignant transformation. In fact, the interval between puberty and FFTP has long been recognized as the "susceptibility window," during which the largely undifferentiated lobular structures in the breast (where virtually all breast tumors arise) are most vulnerable to carcinogens.[71] Hence, for example, cigarette smoking while the "window" is open (i.e., before FFTP) increases long-term breast cancer risk more than smoking after FFTP[72,73] Induced abortion–especially before FFTP—abrogates the long-term risk reduction effected by FTP (as well as eliminating the possibility of breastfeeding, which is also protective).

The independent effect of induced abortion, i.e., comparing the effect of induced abortion to the effect of "never having had that pregnancy"[3] is the typical epidemiological comparison (though an artificial distinction in the clinical sense) and the subject of this review. Strangely, the independent effect has remained controversial despite its emergence in a clear majority of the many studies conducted around the world since 1957.[74] Moreover, the biological basis of the independent effect has become more clearly understood as well, and can be explained by the now well known changes in breast tissue during the course of a normal pregnancy.

Due to rapidly increasing estrogens and progesterone in the maternal circulation, first produced by the ovaries in response to embryonic hCG and subsequently also by the fetoplacental unit, the breasts double in volume by 20 weeks gestation. During this process, the amount of stromal tissue is reduced with a concomitant increase in

ducts and lobules, where breast cancers originate.[71] At 32 weeks gestation, when the placental secretion of human placental lactogen (hPL) has risen to its maximum, breast tissue achieves a level of maturation through well documented epigenetic changes[75] that result in the ability to produce milk. This differentiation renders ducts and lobules resistant to the mutagenic effects of carcinogens and results in a permanent reduction in long-term breast cancer risk.[68]

If a normal pregnancy is abruptly ended through either premature birth or induced abortion before 32 weeks, it will necessarily leave a woman with more undifferentiated breast tissue, where cancers can originate, than before the start of the pregnancy, thereby placing her at increased risk.[38,61] (The effect of induced abortion in increasing the risk of very premature birth therefore provides yet another avenue to increase risk secondarily, via the early termination of subsequent pregnancies through premature birth before 32 weeks gestation.[76,77]).

Moreover, in addition to the dose dependence (in terms of number of induced abortions) of the positive association of IA and breast cancer shown by South Asian studies in the present review, a dose-dependence of the positive association in terms of gestational age at the time of induced abortion has also been observed.[38] This would be dose-dependence upon overall exposure to the high levels of estrogen and progesterone during pregnancy; longer gestation up to 20 weeks resulting in greater exposure and consequently more ductules and lobules, where cancers originate.

Importantly, it is also known that spontaneous abortions—which overwhelmingly occur during the first trimester—are associated with low levels of hCG, and consequently low levels of estradiol and progesterone[78] and little or no breast lobular development. It is therefore not surprising that spontaneous abortion has also long been observed not to be associated independently with increased breast cancer risk.[1,4]

Impact on Future Incidence

As in other parts of the developing world, breast cancer is now becoming established as the most common cause of death among middle-aged women in South Asia,[18,27,30] catching up to the industrialized world where this has been the case for over two decades. In the West, cumulative lifetime incidence is in the range of 10-15%. Assuming a relative risk of 1.3 - 1.5 and a prevalence of approximately 30%, attributable risk is in the range of 10-15%, sufficient to make induced abortion the single best predictor of breast cancer incidence in at least eight European countries.[79] Similar findings have clearly emerged in China,[3] where the institution of the "one child policy" in 1980 made induced abortion commonplace, though almost exclusively after first childbirth.

In South Asia, both breast cancer and induced abortion have been relatively rare until recent years. Since the typical traditional South Asian woman (at least among the rural population) neither drinks nor smokes, marries in her teens, begins having children immediately thereafter, has several children and breastfeeds them all, there are few prevalent risk factors for breast cancer. Hence, baseline incidence is low (cumulative lifetime incidence in the range of 2-3%), and the recently introduced intervention

of induced abortion has little competition among potentially confounding exposures. Hence induced abortion could be expected to produce relatively stronger associations than are seen in the West, as we have observed in the present review (cumulative OR 2.4 – 2.5). We may therefore estimate that the absolute increase in lifetime breast cancer risk attributable to induced abortion is approximately 3% over the baseline risk (i.e., OR 2.5 x 2% baseline cumulative lifetime risk = 5% net cumulative lifetime risk, an absolute risk increase of 3% over 2%; baseline risk being defined as the lifetime risk in the given population due to all other factors besides induced abortion), quite similar to what is seen in the West (i.e., OR = 1.3 x 10% baseline cumulative lifetime risk = 13% net cumulative lifetime risk, an absolute risk increase of 3% over 10%). This is the expected result if induced abortion is truly an independent risk factor for breast cancer.

To obtain a most conservative projection of future impact on the more than 800 million females now alive in South Asia, we assume a 21.5% prevalence of induced abortion (mean prevalence observed among included studies in the present report) and an absolute lifetime breast cancer risk increase of 3%. We thus obtain an estimated 5.16 million South Asian women now alive who will have been diagnosed with breast cancer in their lifetimes. With a current mortality rate of approximately 50%[80] (compared to about 20% in the West[81]), over 2.5 million South Asian females alive today can be expected to die of breast cancer attributable to induced abortion.

Conclusions

It has now been more than six decades since the first peer-reviewed evidence of induced abortion as a breast cancer risk factor appeared in the large nationwide study in Japan by Segi et al.,[82] two decades since the first review and meta-analysis of worldwide studies reported an overall significant link in worldwide studies,[1] and one decade since Carroll's revelation of induced abortion as the single best predictor of breast cancer incidence in Europe.[79] The present report documents the substantial literature of at least 20 new studies published just within the last decade in South Asia alone, summarizing a significant and moderately strong, dose-dependent association between abortion and breast cancer. This association emerges across a diverse array of study populations and designs, and it is supported by now substantial understanding of the biological mechanisms that undergird it.

Nevertheless, health ministries in the US and around the world, as well as medical associations and even voluntary anti-cancer organizations echo messages of denial of any effect of induced abortion on breast cancer risk. For example, the current guidance of the US National Cancer Institute flatly states: "Women who have had an induced abortion have the same risk of breast cancer as other women" (available at: https://www.cancer.gov/about-cancer/causes-prevention/risk/hormones/reproductive-history-fact-sheet#q4[83]). Instead, abortion is still touted as a safe procedure, and even the World Health Organization does not list abortion as a risk factor, even though breast cancer is now the most common cause of cancer death for women worldwide.[22] Continuing denial of abortion's effect on breast cancer risk can only ensure that the acknowledged worldwide breast

cancer epidemic will continue to worsen, costing many millions of women their lives over the next several decades.

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