Articles

Breast cancer and abortion: collaborative reanalysis of data from 53 epidemiological studies, including 83 000 women with breast cancer from 16 countries

*Collaborative Group on Hormonal Factors in Breast Cancer**

Summary

Background The Collaborative Group on Hormonal Factors in Breast Cancer has brought together the worldwide epidemiological evidence on the possible relation between breast cancer and previous spontaneous and induced abortions.

Methods Data on individual women from 53 studies undertaken in 16 countries with liberal abortion laws were checked and analysed centrally. Relative risks of breast cancer—comparing the effects of having had a pregnancy that ended as an abortion with those of never having had that pregnancy—were calculated, stratified by study, age at diagnosis, parity, and age at first birth. Because the extent of under-reporting of past induced abortions might be influenced by whether or not women had been diagnosed with breast cancer, results of the studies—including a total of 44 000 women with breast cancer—that used prospective information on abortion (ie, information that had been recorded before the diagnosis of breast cancer) were considered separately from results of the studies—including 39 000 women with the disease—that used retrospective information (recorded after the diagnosis of breast cancer).

Findings The overall relative risk of breast cancer, comparing women with a prospective record of having had one or more pregnancies that ended as a spontaneous abortion versus women with no such record, was 0·98 (95% CI 0·92–1·04, p=0·5). The corresponding relative risk for induced abortion was 0·93 (0·89–0·96, p=0·0002). Among women with a prospective record of having had a spontaneous or an induced abortion, the risk of breast cancer did not differ significantly according to the number or timing of either type of abortion. Published results on induced abortion from the few studies with prospectively recorded information that were not available for inclusion here are consistent with these findings. Overall results for induced abortion differed substantially between studies with prospective and those with retrospective information on abortion (test for heterogeneity between relative risks: χ^2_1=33·1, p<0·0001).

Interpretation Pregnancies that end as a spontaneous or induced abortion do not increase a woman's risk of developing breast cancer. Collectively, the studies of breast cancer with retrospective recording of induced abortion yielded misleading results, possibly because women who had developed breast cancer were, on average, more likely than other women to disclose previous induced abortions.

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*Collaborators listed at http://image.thelancet.com/extras/04art2192webappendix.pdf

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Introduction

Pregnancies that result in a birth are known to reduce a woman's long-term risk of developing breast cancer,[1] but the effects of pregnancies that end as a spontaneous or, particularly, as an induced abortion are less clear, although many studies have relevant data.[2–60] The findings from case-control studies—in which women were asked their abortion history after they were diagnosed with breast cancer—have been especially difficult to interpret. For, women who have had an induced abortion are known to under-report such events,[61–63] but they might be more likely to disclose this information than they would otherwise have been if they had been diagnosed with breast cancer and knew that they were taking part in a research project investigating the causes of their disease.[62] Hence, in case-control studies in which "cases" are women with recently diagnosed breast cancer and "controls" are women who do not have the disease, and in which information on past abortions is obtained retrospectively (ie, after the cases have been diagnosed with breast cancer), the extent of under-reporting of induced abortion might well differ between the cases and controls. For example, among women in a Swedish case-control study[62] who had, in fact, had a previous induced abortion recorded on a national abortion register, 21% of those with breast cancer and 27% of those without the disease reported incorrectly that they had never had an induced abortion. Any such systematic differences between women with and without breast cancer in the under-reporting of past induced abortions could appreciably distort the results from studies with retrospectively recorded information on abortion,[62] but could not similarly affect results from studies in which the information on abortion had been recorded prospectively, that is, before the diagnosis of breast cancer.

One of the goals of the Collaborative Group on Hormonal Factors in Breast Cancer, when it was set up in 1992, was to combine the worldwide epidemiological evidence on the relation between breast cancer and reproductive events, including pregnancies that end as abortions. Because, as noted above, differential retrospective reporting of induced abortion between cases and controls could have taken place, results of the studies with retrospectively obtained records of abortion are presented in this report separately from results of the studies with prospective records that predated the diagnosis of breast cancer.

Methods

Contributing studies and collection of data

Epidemiological studies were eligible for inclusion if they had (before any exclusions) 100 or more women with incident invasive breast cancer, were undertaken in countries with liberal abortion laws,[61] and had systematically sought information about every woman on reproductive history, including details about previous

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spontaneous and induced abortions. Potentially eligible studies were identified from review articles, computer-aided literature searches done up to October, 2003, with MEDLINE, EMBASE and PubMed, and discussions with colleagues. Efforts were made to identify studies that recorded information on abortion, whether or not results had been published.

61 eligible studies were identified, 58 of which had published some findings,[2–60] although not necessarily on abortion. Another four studies[64–67] that had reported on breast cancer in relation to abortion were ineligible, because specific information on whether pregnancies ended as spontaneous or induced abortions had not been recorded systematically for women with breast cancer and a comparison group. Attempts were made to contact principal investigators of each of the 61 eligible studies, inviting them to join the collaboration and to contribute individual data centrally, so that similar definitions could be used across studies. Principal investigators of four studies[53–56] could not be traced; original data could not be retrieved by the principal investigators of three studies;[57–59] and only one group of researchers[60] declined to take part in the collaboration. Investigators from the remaining 53 eligible studies participated in the collaboration. 13 of the 53 studies had recorded information on abortion prospectively by record linkage or cohort designs. Individual data from 12 of these studies were contributed using a nested case-control approach, in which up to four controls per case were selected at random, matched by age at diagnosis and broad geographic region. For the multicentre European Prospective Investigation into Cancer and Nutrition (EPIC), data from three centres[48,51,52] are currently available, including about two-thirds of the potentially eligible women with breast cancer in all centres combined. In the remaining study with prospectively obtained information on abortion,[34] data were contributed as observed numbers of cases and of person-years at risk, according to the strata used in these analyses. That study linked information from the Danish register of induced abortion to national cancer registry data, but had no information on pregnancies ending as spontaneous abortions.

The methods of data collection, checking, and correction have been described elsewhere.[68] Data sought included anonymised information on every woman's total number of pregnancies, on her age at every pregnancy, and on whether or not every pregnancy had ended as a birth, as a spontaneous abortion, or as an induced abortion. A woman's parity was taken to be the total number of livebirths and stillbirths she had had (twins, triplets, etc, counted as one birth). In some studies, details of past births did not include stillbirths, and for those studies a woman's parity was taken to be the total number of livebirths. Every investigator was asked how the recorded information on abortion had been obtained (self-reported, or from an abortion register or other medical record) to ascertain whether the occurrence of the abortion had been recorded objectively in a medical or related record. Investigators were also asked whether the information on abortion was recorded prospectively or retrospectively—ie, before or after the date of diagnosis of breast cancer for the cases and the date of pseudodiagnosis for the controls. Collaborators requested a priori that if principal investigators judged their own information on induced abortion to be unreliable, they could ask that their data be excluded from the analyses: investigators of one retrospective study,[31] including 1% of the total number of women with breast cancer, did so. The possible bias associated with excluding data from this study is discussed later.

Collaborators agreed a priori that, to minimise possible differential reporting of illegal abortion, analyses should be restricted, as far as possible, to populations with access to legal abortion services. To define precisely when, in a given country, women of reproductive age would have had access to legal abortion services is not straightforward, and the following were taken to be the years in which such services would have become available:[61] 1937 (for Sweden), 1938 (Denmark), 1945 (Norway), 1957 (China), 1967 (UK), 1969 (Australia and Canada), 1970 (Canton of Vaud, Switzerland, where a progressively more liberal interpretation of the legislation restricting pregnancy termination has been applied since the early 1970s; Levi F, Lausanne University, personal communication), 1972 (former German Democratic Republic), 1973 (USA), 1974 (former Yugoslavia), 1975 (France), 1978 (Israel and Italy), 1979 (New Zealand), 1981 (Netherlands), and 1988 (Greece). Women who were past their reproductive period—ie, aged 50 years or older, by the calendar years specified above—were excluded from the analyses. However, induced abortions reported by women who were younger than age 50 years at the time may not necessarily have been legal, and so sensitivity analyses were done, excluding women aged 40 years or older rather than aged 50 years or older.

Statistical analysis

To ensure that women in one study were compared directly only with similar women in the same study, all analyses were routinely stratified by study, by centre within study, by fine divisions of age at diagnosis (16–64 in single years, and 65–89 in 5-year age-groups), by parity and, where appropriate, by women's age when their first child was born (nulliparous women were included as a separate stratum and parous women were cross-classified by parity [1–2, 3–4, 5–6, ⩾7, unknown] and age at first birth [<20, 20–24, 25–29, >30 years, unknown]). Parity and age at first birth were incompletely recorded in four studies, and sensitivity analyses were done to assess the possible magnitude of confounding by these factors. Data from different strata were combined by the Mantel-Haenszel technique—the stratum-specific quantities calculated being the usual observed minus expected (O–E) numbers of women with breast cancer and their variances.[69,70] Summation of every stratum-specific quantity in a study yields the stratified O–E value for that study and summation of their variances yields its variance, var(O–E). Results from several studies can likewise be combined by summation of their O–E values and their variances. For the Danish record-linkage study that provided only stratum-specific observed numbers and person-years,[34] values equivalent to O–E and its variance were calculated.

Either for an individual study or for a combination of several studies, the O–E value and its variance yield not only statistical tests (two-sided p values) but also statistical descriptions (odds ratios, subsequently referred to as relative risks). These come from the one-step formula: the log of the relative risk is calculated as (O–E)/var(O–E).[69,70] The overall log relative risk for a combination of several studies is thus an inverse-variance-weighted average of the log relative risk of every separate study. Hence, the overall relative risk is, effectively, a weighted average of the contributory relative risks. Although this approach is sometimes called the "fixed effect" method of meta-analysis, it is better referred to as the "assumption free" method,[71] since it avoids any assumption of homogeneity. Heterogeneity tests involve summation of $(O–E)^2/var(O–E)$.[71] Results are presented as the relative risks of breast cancer associated with having

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	Country	Study design*	Source of information about abortion	Median year of diagnosis of breast cancer	Number of women with/without breast cancer		
					All women	With a record of spontaneous abortion	With a record of induced abortion
13 studies with information on abortion recorded prospectively—ie, before the diagnosis of breast cancer							
Melbye[34]	Denmark	Record-linkage	Abortion register	1973–92	10 062/†	–	1338/–
Oxford/FPA[14]	UK	Cohort	Self-reported	1982	197/779	47/157	5/18
Goldacre[44]	England	Record-linkage	Hospital admission	1986	21 847/84 464	106/506	315/1576
Guernsey[35(2 studies)]	UK	Cohort	Self-reported	1987	99/395	28/82	6/15
Erlandsson[49]	Sweden	Record-linkage	Self-reported	1988	1759/1759	229/282	173/228
RCGP[9]	UK	Cohort	General practitioner	1988	1068/4437	58/228	48/223
Iowa Women's[41]	USA	Cohort	Self-reported	1991	626/2490	178/708	6/31
Tang[43]	USA	Record-linkage	Self-reported	1992	461/2178	158/730	95/477
Newcomb[42]	USA	Record-linkage	Hospital admission	1994	138/252	26/45	23/44
Scotland[(unpublished)]	Scotland	Record-linkage	Hospital admission	1994	2885/10 073	253/908	511/2237
Shanghai textiles[46]	China	Cohort	Self-reported	1995	1893/7572	222/927	884/3631
EPIC[51,52,48]	France/Greece/UK	Cohort	Self-reported	1996	2891/4089	657/891	583/755
40 studies with information on abortion recorded retrospectively—ie, after the diagnosis of breast cancer							
Pike/Bernstein[2]	USA	Population controls	Self-reported	1974	163/270	13/9	11/8
Morabia[23]	USA	Hospital controls	Self-reported	1974	236/330	75/91	15/22
Brinton[3]	USA	Population controls	Self-reported	1976	1448/1627	412/475	25/27
Modan[6]	Israel	Hospital controls	Self-reported	1977	339/608	166/309	99/173
Vessey[7]	UK	Hospital controls	Self-reported	1977	1109/1116	257/281	75/81
CASH[19]	USA	Population controls	Self-reported	1981	4446/4668	1132/1345	333/324
Hislop[5]	Canada	Population controls	Self-reported	1981	677/702	164/179	67/55
Ravnihar[10]	Slovenia‡	Hospital controls	Self-reported	1981	531/1939	98/381	177/650
WHO[24]	4 countries§	Hospital controls	Self-reported	1982	1719/4661	385/1083	661/1488
Ewertz[8]	Denmark	Population controls	Self-reported	1983	1507/1381	277/223	207/169
Lê[4]	France	Hospital controls	Self-reported	1983	265/265	52/62	81/62
Rohan[11]	Australia	Population controls	Self-reported	1983	333/330	75/75	17/7
UK National[13]	UK	Population controls	Self-reported	1983	755/755	123/137	103/91
Clarke[20]	Canada	Population controls	Self-reported	1984	547/1098	132/279	44/74
Clavel[16]	France	Hospital controls	Self-reported	1984	495/896	98/187	83/117
Long Island[18]	USA	Population controls	Self-reported	1984	763/762	222/210	63/49
Meirik/Lund[15]	Sweden/Norway	Population controls	Self-reported	1984	422/527	87/98	73/100
Yuan/Yu[12]	China	Population controls	Self-reported	1984	534/534	102/98	187/193
Paul/Skegg[38]	New Zealand	Population controls	Self-reported	1985	889/1862	242/481	30/64
Wang/Yu[21]	China	Population controls	Self-reported	1985	300/300	50/50	134/163
Bernstein[50]	USA	Population controls	Self-reported	1986	676/676	126/128	177/181
La Vecchia[17]	Italy	Hospital controls	Self-reported	1986	2171/1759	447/364	260/237
Daling/Malone[25]	USA	Population controls	Self-reported	1987	747/961	166/229	187/200
4 State study[30]	USA	Population controls	Self-reported	1988	4572/6766	1201/1678	173/255
CR-UK[(unpublished)]	UK	Population controls	Self-reported	1988	644/644	160/140	86/89
Ross/Paganini-Hill[36]	USA	Population controls	Self-reported	1988	1040/991	281/304	83/65
Rookus/van Leeuwen[31]	Netherlands	Population controls	Self-reported	1988	912/913	190/194	56/36¶
Primic-Zakelj[27]	Slovenia‡	Population controls	Self-reported	1989	624/624	110/107	247/243
Stanford/Habel[32]	USA	Population controls	Self-reported	1989	450/492	144/135	29/34
Yang/Gallagher[22]	Canada	Population controls	Self-reported	1989	877/885	213/211	74/67
Katsouyanni[26]	Greece	Hospital controls	Self-reported	1990	297/638	77/160	158/276
UK ICRF[(unpublished)]	UK	Population controls	Self-reported	1991	472/472	117/118	55/47
WISH[28]	USA	Population controls	Self-reported	1991	1866/2009	402/479	405/412
Franceschi[33]	Italy	Hospital controls	Self-reported	1992	2014/1968	410/456	276/218
Levi[29]	Switzerland	Hospital controls	Self reported	1992	242/491	68/87	52/78
McCredie/Hopper[37]	Australia	Population controls	Self-reported	1993	466/408	98/85	81/46
Chang-Claude[47]	Germany	Population controls	Self-reported	1994	656/1283	111/202	97/144
Millikan[40]	USA	Population controls	Self-reported	1994	816/756	205/228	101/78
McCredie/Hopper[39]	Australia	Population controls	Self-reported	1996	1114/613	259/158	179/74
Shu/Zheng[45]	China	Population controls	Self-reported	1997	1459/1556	159/177	913/998

*For case-control studies with retrospectively recorded information on abortion, the source of controls is given. †Not given for this study (see text). ‡Formerly Yugoslavia. §Australia, China, Germany, Israel. ¶Published numbers for women with/without breast cancer.[31]

Description of studies included in analyses of the risk of breast cancer after abortion

had one or more pregnancies end as an abortion, compared with never having had such a pregnancy. The analyses presented here are, where possible, stratified by parity and age at first birth. This stratification allows for both the effects of previous reproductive history on the probability of having an abortion and the extent to which having had an abortion alters a woman's subsequent reproductive history.

Where results are presented as plots, with every black square representing the value of a relative risk, the area of the square is proportional to var(O–E). Hence, the area of the black square is inversely proportional to the variance of the log of the relative risk, thereby providing an indication of the amount of statistical information available for that particular relative risk estimate.[71] Results are presented separately for studies with prospective and retrospective records of abortion. Within both these categories of study design, results are shown separately for every study in which var(O–E) was more than 20 (implying that the variance of the log relative risk is less than 1/20) and results from the smaller studies are combined. Study-specific data are presented in such a way that readers can combine results from individual studies in whichever way they choose: the method for doing so is described in appendix 13 of a previous report.[68]

Role of the funding source

The sponsors of the study had no role in the study design, data collection, data analysis, data interpretation, or writing of the report.

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Results

The table contains details of the 53 studies from 16 countries that were available for analysis, which contribute a total of 83 000 women with breast cancer. Studies are grouped according to whether information on abortion was recorded prospectively (44 000 women with breast cancer) or retrospectively (39 000 women with breast cancer). Within each type of study design, individual studies are listed chronologically, according to the median year of diagnosis of breast cancer in the study population. Of the 13 studies with prospective records on abortion, five (four published[9,34,42,44] and the unpublished Scottish study) used objective information from abortion registers, general practitioner records, or hospital admissions for abortion. On average, the age of the women with breast cancer was 50·4 years and they had had 2·4 births.

For spontaneous abortion, figure 1 shows the study-specific results and the combined results separately for studies with prospectively and retrospectively recorded information on abortion. Results from only 12 of the 13 studies with prospectively recorded information are available because information on spontaneous abortion had not been recorded in one of the studies.[34] The relative risks for these 12 studies (upper part of figure 1) vary around unity (1·0), and the weighted average of them (see Methods) yields an overall relative risk of 0·98 (95% CI 0·92–1·04; p=0·5). This finding means that, on average, the risk of breast cancer in women with prospective records of having had one or more pregnancies end as a spontaneous abortion does not differ significantly from that in women with no record of such a pregnancy. Among these studies, no significant variation was found between those with objective and those with self-reported information on spontaneous abortion (relative risks [RR] 0·95 [95% CI 0·85–1·07] and 0·99 [0·92–1·06], respectively; χ^2_1 for heterogenity=0·3, p=0·6). Further, no significant variation was found between the results in studies that had recorded information on spontaneous abortions prospectively and those that had done so retrospectively (shown in the upper and lower part of figure 1, respectively; χ^2_1 for heterogenity=0·01, p=0·9).

For induced abortion, figure 2 shows the study-specific results and the combined results separately for studies with prospectively and retrospectively recorded information on abortion. Relative risks for the 13 studies with prospectively recorded information (upper part of figure 2) are close to, or slightly below, unity, and the weighted average of them yields an overall relative risk of 0·93 (95% CI 0·89–0·96; p=0·0002). Hence, neither the results from the individual studies nor their weighted average suggest any adverse effect on the subsequent risk of breast cancer for women with prospective records of having had one or more pregnancies that ended as an induced abortion, compared with women having no record of such a pregnancy. Furthermore, among the studies with prospective records of induced abortion, no significant variation in the results was found between those with objective and those with self-reported information (RR 0·93 [95% CI 0·88–0·97] and 0·92 [0·85–0·99], respectively; χ^2_1 for heterogeneity=0·04, p=0·8).

However, a substantial difference was seen between the overall estimate of relative risk from studies that had recorded information on induced abortion prospectively and the overall estimate of relative risk from studies that had recorded such information retrospectively (upper *vs* lower part of figure 2). The variation in the weighted average relative risks between these two types of study design was highly significant (χ^2_1 for heterogeneity=33·1, p<0·0001). This difference, according to whether information about abortion was recorded before or after the diagnosis of breast cancer, could not be accounted for by any known differences between the women included in each type of study, and suggests that the systematic difference in reporting induced abortion between cases and controls indicated by the Swedish retrospective study[62] also occurred in some of the other studies with retrospectively obtained information on abortion. Because prospective records of induced abortion, which predate any diagnosis of breast cancer, are not subject to the type of differential recording that can occur retrospectively because of reverse causality, most weight is given subsequently to results from studies that had recorded abortion history prospectively.

For the effects of a pregnancy that ended in a spontaneous abortion, the relative risks of breast cancer in studies with prospectively recorded information on abortion were 0·89 (95% CI 0·80–0·98) for cancers diagnosed before age 45 years and 1·03 (0·96–1·12) for those diagnosed at older ages. For an induced abortion, the corresponding relative risks were 0·92 (0·87–0·97) and 0·93 (0·88–0·99). Among nulliparous women the relative risks were 1·01 (0·72–1·41) and 1·01 (0·85–1·22), respectively, for spontaneous and induced abortion, and in parous women the corresponding relative risks were 0·96 (0·90–1·03) and 0·93 (0·89–0·97). Both for spontaneous and for induced abortions, the relative risk did not differ significantly in relation to the number of abortions, the woman's age at abortion, or time since the abortion (figure 3). All but one[34] of the 13 studies with prospectively recorded information had data both on spontaneous and on induced abortions. When—in the remaining 12 studies—women who had no record of a pregnancy ending as either a spontaneous or an induced abortion were used as the comparison group, the estimated relative risk of breast cancer for having had a pregnancy end as either type of abortion was 0·91 (0·86–0·95, p<0·0001).

To minimise potential confounding by parity and age at first birth, analyses were stratified by these factors wherever possible, but four studies with prospectively obtained information on abortion (three published[9,43,44] and the unpublished Scottish study) did not have complete information on these factors. To assess the importance of parity and age at first birth as confounding factors, analyses were undertaken of the other studies, adjusting and not adjusting for both variables. When this was done (in the studies with prospectively obtained complete information on both factors), the adjusted and unadjusted relative risks were, respectively, 0·98 and 0·95 for spontaneous abortion and 0·97 and 0·94 for induced abortion, suggesting for both types of abortion that adjustment for these reproductive variables would generally multiply the relative risk by a factor of about 1·03. Correction of results in the four studies by such a factor would multiply the relative risks for the weighted average of all studies with prospectively recorded information by about 1·01.

The effect of eight other potential confounding factors was examined in studies with prospectively collected information on abortion. Since not all studies had obtained information on all eight potential confounding factors considered, the effect of adjustment for each of them on the relative risk of breast cancer was examined by stratifying for that factor in the studies that had collected relevant information. Stratification in turn by socioeconomic status or education, ever use of oral

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Study (country)	Spontaneous abortion recorded (cases/controls)	No spontaneous abortion recorded (cases/controls)	O–E	Var(O–E)	RR* (99% CI)	RR* (SE)
12 studies with information on abortion recorded prospectively—ie, before the diagnosis of breast cancer						
Oxford/FPA (UK)[14]	47/157	150/622	4·6	21·2		1·24 (0·243)
Goldacre (UK)[44]	106/506	21 741/83 958	−18·0	92·9		0·82 (0·094)
Erlandsson (Sweden)[49]	229/282	1530/1477	−26·3	98·3		0·77 (0·088)
RCGP (UK)[9]	58/228	1010/4209	1·0	37·7		1·03 (0·165)
Iowa Women's Health (USA)[41]	178/708	448/1782	3·2	93·5		1·03 (0·105)
Tang (USA)[43]	158/730	301/1445	2·9	80·7		1·04 (0·113)
Scotland (UK)[unpublished]	253/908	2575/8873	1·5	172·8		1·01 (0·076)
Shanghai Textile Workers (China)[46]	222/927	1671/6645	−5·6	149·8		0·96 (0·080)
EPIC (France/Greece/UK)[48,51,52]	657/891	2324/3198	7·4	242·1		1·03 (0·065)
Other[35(2 studies),42]	54/127	183/520	5·5	14·1		1·48 (0·326)
All studies with prospective data	**1962/–**	**31 933/–**	**–23·8**	**1003·1**		0·98 (0·031)
40 studies with information on abortion recorded retrospectively—ie, after the diagnosis of breast cancer						
Brinton (USA)[3]	412/475	1036/1152	−0·4	138·8		1·00 (0·085)
Modan (Israel)[6]	166/309	173/299	−2·3	37·9		0·94 (0·158)
Vessey (UK)[7]	257/281	852/835	−4·0	82·5		0·95 (0·107)
CASH (USA)[19]	1132/1345	3313/3321	−52·6	406·8		0·88 (0·047)
Hislop (Canada)[5]	164/179	513/523	−1·3	45·0		0·97 (0·147)
Ravnihar (Slovenia)[10]	98/381	433/1558	−3·1	59·7		0·95 (0·126)
WHO (4 countries, see table 1)[24]	385/1083	1334/3578	−28·1	165·6		0·84 (0·071)
Ewertz (Denmark)[8]	277/223	1226/1157	20·1	87·3		1·26 (0·120)
UK studies (UK)[13 and 2 unpublished]	400/395	1471/1476	8·3	138·7		1·06 (0·088)
Clarke (Canada)[20]	132/279	415/819	−4·5	50·3		0·91 (0·135)
Clavel(France)[16]	98/187	397/709	0·2	40·0		1·01 (0·159)
Long Island (USA)[18]	222/210	541/552	8·4	61·5		1·15 (0·137)
Meirik/Lund (Sweden/Norway)[15]	87/98	335/429	1·9	30·7		1·06 (0·186)
Yu/Yuan/Wang (China)[12,21]	152/148	682/686	1·7	40·2		1·04 (0·161)
Paul/Skegg (New Zealand)[38]	242/481	647/1381	−7·9	93·4		0·92 (0·099)
Bernstein (USA)[50]	126/128	550/548	−1·1	39·0		0·97 (0·158)
La Vecchia/Franceschi (Italy)[17,33]	857/820	3328/2906	−20·5	277·1		0·93 (0·058)
Daling/Malone (USA)[25]	166/229	581/732	−8·0	59·5		0·87 (0·121)
4 State Study (USA)[30]	1201/1678	3371/5088	34·4	414·3		1·09 (0·051)
Ross/Paganini-Hill (USA)[36]	281/304	759/687	−8·2	86·8		0·91 (0·102)
Rookus/van Leeuwen (Netherlands)[31]	190/194	723/718	5·2	64·6		1·08 (0·130)
Primic-Zakelj [27]	110/107	514/517	−2·2	37·8		0·94 (0·158)
Stanford/Habel (USA)[32]	144/135	306/357	14·1	38·1		1·45 (0·196)
Yang/Gallagher (Canada)[22]	213/211	663/673	1·2	61·4		1·02 (0·129)
Katsouyanni (Greece)[26]	77/160	220/478	−2·9	29·0		0·90 (0·177)
WISH (USA)[28]	402/479	1464/1530	−19·1	142·5		0·87 (0·078)
McCredie/Hopper (Australia)[37,39]	357/243	1223/778	−4·0	83·3		0·95 (0·107)
Chang-Claude (Germany)[47]	111/202	545/1081	6·8	47·3		1·15 (0·156)
Millikan (USA)[40]	205/228	610/528	−8·9	58·3		0·86 (0·121)
Shu/Zheng (China)[45]	159/177	1300/1379	−3·3	66·3		0·95 (0·120)
Other[2,4,11,23,29]	283/324	955/1361	19·1	70·1		1·31 (0·137)
All studies with retrospective data	**9106/11 693**	**30 480/37 836**	**−61·0**	**3053·8**		0·98 (0·018)

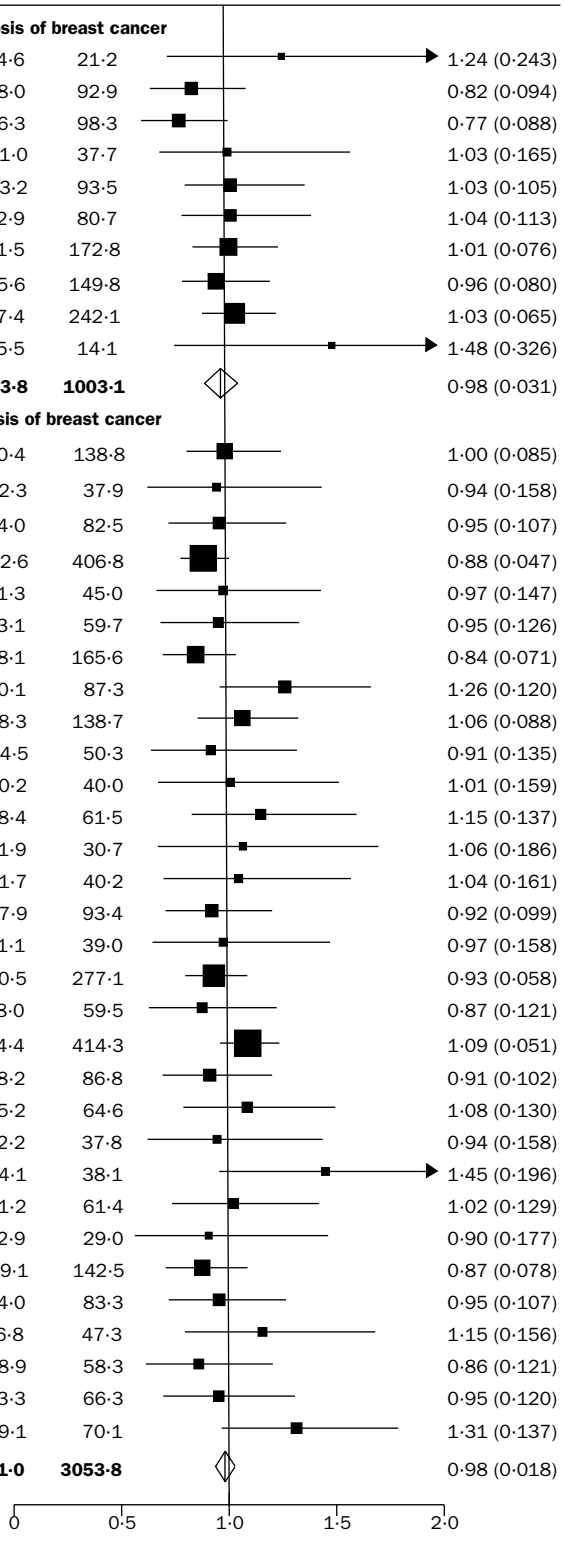

Figure 1: **Relative risk of breast cancer, comparing the effects of having had a pregnancy that ended as a spontaneous abortion versus effects of never having had that pregnancy**

Four of the studies with prospective data had objective information on abortion (references 9, 42, 44, and the unpublished study from Scotland). *Stratified by study, age, and where possible, parity and age at first birth (see Methods). Tests for heterogeneity: between studies with prospective data, χ^2_{11}=15·7, p=0·2; between studies with retrospective data, χ^2_{39}=55·4, p=0·05; and between studies with prospective and retrospective data, χ^2_1=0·01, p=0·9.

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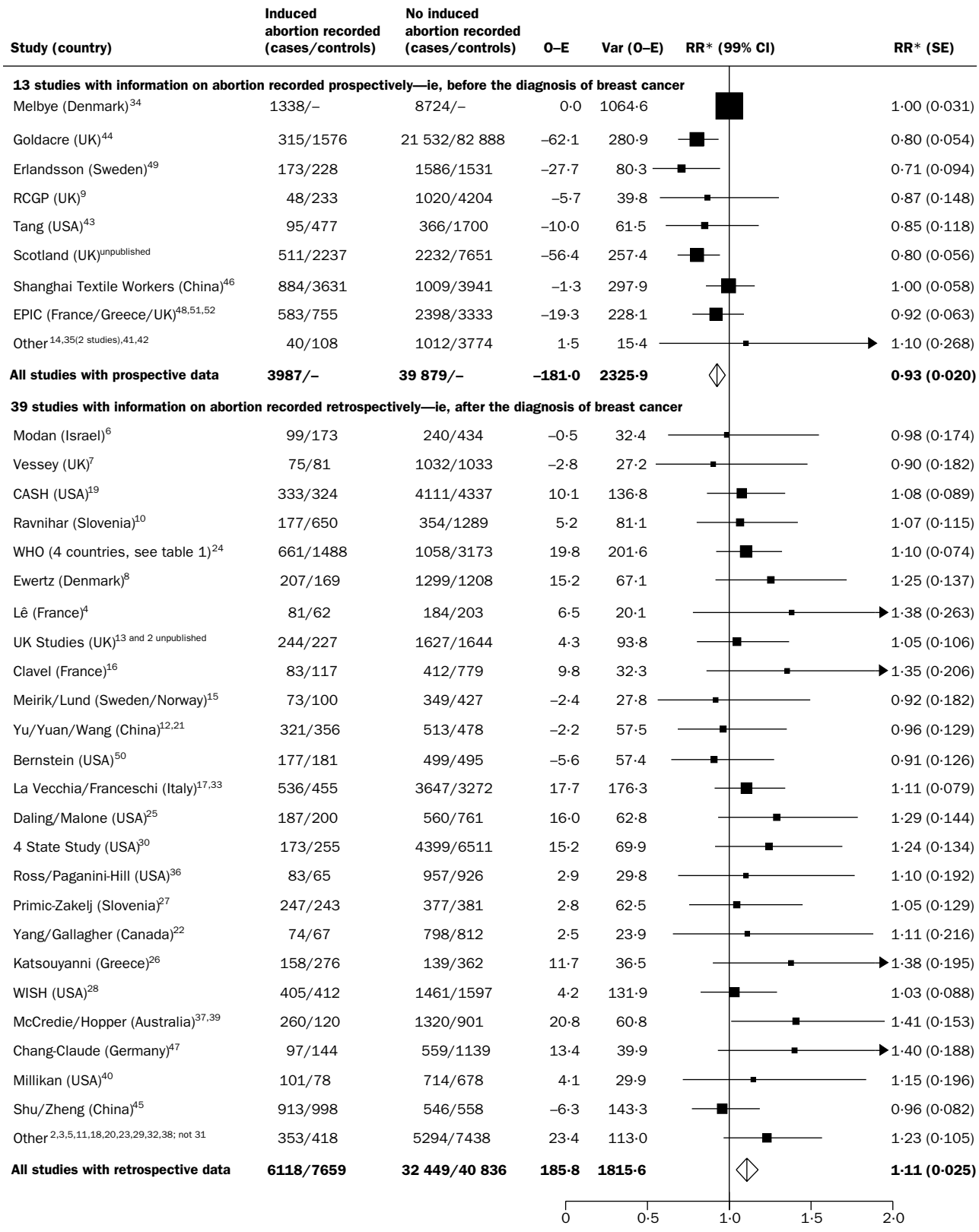

Figure 2: **Relative risk of breast cancer, comparing the effects of having had a pregnancy that ended as an induced abortion versus effects of never having had that pregnancy**

Five of the studies with prospective data had objective information on abortion (references 9, 34, 42, 44, and the unpublished study from Scotland). *Stratified by study, age, and where possible, parity and age at first birth (see Methods). Tests for heterogeneity: between studies with prospective data, χ^2_{12}=27·0, p=0·008; between studies with retrospective data, χ^2_{38}=37·6, p=0·5; and between studies with prospective and retrospective data, χ^2_1=33·1, p<0·0001.

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contraceptives, breastfeeding, age at menarche, weight, alcohol consumption, menopausal status, and family history of breast cancer (in the studies with prospectively obtained information) altered the relative risk associated with having had one or more spontaneous abortions compared with none by multiplying factors of 0·99, 0·98, 1·01, 1·00, 0·97, 1·02, 0·97, and 1·00, respectively, and altered the relative risk associated with having had one or more induced abortions by multiplying factors of 0·94, 0·99, 1·00, 0·99, 1·01, 1·01, 0·99, and 1·00, respectively.

While objective records of induced abortions generally relate to legal abortion, self-reported induced abortions could be either legal or illegal, and the information obtained by principal investigators did not usually distinguish between the two. Women were excluded from all foregoing analyses if they were too old to have been pregnant after the abortion laws were liberalised, and the study-specific numbers and relative risks presented here are, thus, not necessarily identical to those published for every study. Nevertheless, some women included here would not have had access to legal abortion services for at least part of their reproductive years. When analyses were further restricted to women younger than 40 years when the country-specific abortion laws were liberalised, the resultant relative risk of breast cancer associated with one or more induced abortions, compared with none, was virtually unchanged at 0·92 (95% CI 0·89–0·96) in studies with prospectively recorded information. However, even with these further restrictions, some women still could have been at risk of illegal abortion for part of their reproductive lives.

Of the eight published studies that did not contribute at all to this collaboration[53–60] only two had recorded information on abortion history prospectively.[58,59] These two studies included 1516 women with breast cancer (only 3% as many women with breast cancer as in such studies that did contribute), and in them the combined relative risk for one or more induced abortions compared with none was 0·99 (95% CI 0·89–1·11). When the published results from these two studies were combined with the present results from the other studies with prospectively recorded information (upper part of figure 2), the overall relative risk was still 0·93 (0·89–0·97). For the studies with retrospective information not included here that had published relevant data (including published results from the one participating study that principal investigators requested be excluded from these analyses),[31] the combined estimate of the relative risk of breast cancer associated with one or more reported induced abortions was 1·39 (1·22–1·57); and when those published results were combined with the present results from the studies with retrospectively recorded information (lower part of figure 2), the overall relative risk was 1·14 (1·09–1·19).

Discussion

An advantage of seeking to review all available studies of breast cancer and abortion is that this helps avoid unduly selective emphasis on particular studies, or just on published results. Only about two-thirds of the eligible studies that had obtained relevant information had published their findings on abortion and breast cancer.[2–60] Hence, reviews based solely on previous published work could have been susceptible to publication bias as well as to the biases associated with differential reporting of abortion in studies with retrospectively obtained information.[72–83] The two published studies[58,59] with prospective records on the risk of breast cancer after induced abortion that are not included here contain only 3% as many women with breast cancer as those that were included: failure to include these two small studies would not materially alter the overall findings. Unpublished data from one large prospective study[84] was not included, because only at a late stage of the review process was it found out that information on abortion had been obtained after that study had begun. Despite extensive efforts to identify studies with unpublished results, to guarantee that others do not exist is clearly impossible. Furthermore, to have completely up-to-date information from continuing prospective studies such as EPIC,[48,51,52] which are accumulating data beyond the time when information was contributed to this collaboration, is not possible. Unpublished results from known continuing prospective

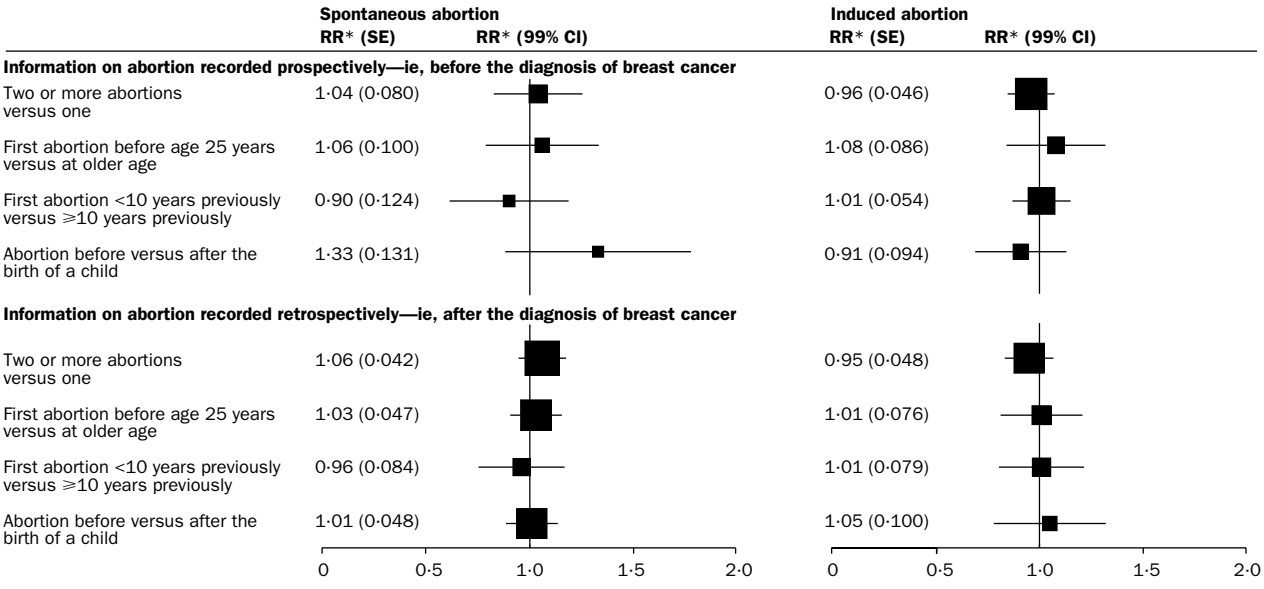

Figure 3: **Relative risk of breast cancer in relation to number and timing of pregnancies that ended in abortion**
*Stratified by study, age, and where possible, parity and age at first birth.

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studies contain at least another 5% as many women with breast cancer as are included here, but there is no good reason to expect that over the next few years inclusion of additional data from such studies will materially alter the evidence that is already available.

This international collaborative reanalysis of individual data on 83 000 women with breast cancer from 53 studies found substantial and highly significant variation in the results for induced abortion, but not for spontaneous abortion, between studies that had recorded information on abortion prospectively and retrospectively—ie, before and after the diagnosis of breast cancer. 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.[62] In view of the potential for differential retrospective reporting of past induced abortions to distort the results, and given the highly significant differences found here between the overall findings from the studies that had recorded information on induced abortion retrospectively and prospectively, the collective results from the studies with retrospective records cannot be trusted. The possibility that, on average, women are more likely to disclose previous induced abortions after they are diagnosed with breast cancer than they would otherwise have been cannot be excluded. Hence, in interpreting the worldwide evidence, the chief emphasis should be on the results from studies with prospective information, in which the recording of abortion predated any diagnosis of breast cancer.

Among the 44 000 women with breast cancer included in the 13 studies with prospective information, the aggregate relative risk of breast cancer associated with having a record of one or more pregnancies that ended as an induced abortion compared with having no such record is 0·93 (0·89–0·96), suggesting no significant adverse effects, on average. Furthermore, none of the results from individual studies suggested an adverse effect. Within each of these 13 studies, some under-recording of past induced abortions must have taken place[61–63] and a small amount of over-reporting could also have happened. Both types of misclassification would, however, be statistically independent of whether otherwise similar women subsequently developed breast cancer. If pregnancies that ended as induced abortions had no material effect on the subsequent risk of breast cancer, then neither type of misclassification would be expected to distort the results from studies with prospectively recorded information. If, on the other hand, the overall relative risk of 0·93 indicates a real protective effect of pregnancies that end as induced abortions, then either type of misclassification would tend to dilute the overall findings, so the true relative risk for breast cancer could be slightly lower than the observed value of 0·93. However, if pregnancies that ended as induced abortions did protect against breast cancer, the risk of breast cancer might be expected to vary according to the number and timing of abortion and no such associations were seen (figure 3).

The reliability of reporting of pregnancies that ended as a spontaneous abortion is difficult to assess. Investigators of one participating study in China asked women on two occasions about their history of spontaneous abortion and over 90% agreement was found,[47] and in another study[85] 73% of spontaneous abortions self-reported soon after the event were also reported more than 20 years later. Both under-reporting and over-reporting of early spontaneous abortions can occur,[85] because early miscarriages are difficult to diagnose reliably and can be unrecognised. As far as can be ascertained, no study has compared self-reported information on spontaneous abortion with information from medical records or other objective sources. Nevertheless, if little or no real association between spontaneous abortion and risk of breast cancer exists then any misclassification of women should not much affect the overall results, and the relative risk of breast cancer associated with having a record of one or more pregnancies that ended as a spontaneous abortion, compared with no such record, is 0·98 (0·92–1·04) for all studies with prospectively recorded information.

Because—in studies with prospectively recorded information—unbiased under-recording (or, indeed, over-recording) of abortion should not greatly distort the overall findings, relative risks should not differ much between studies using objective sources and those using self-reported information on abortion, and in fact they did not (relative risks of 0·95 and 0·99, respectively, for spontaneous abortion, and 0·92 and 0·93, respectively, for induced abortion). Studies using abortion registers, medical records, and other objective sources have some advantages over studies using self-reported data, in that the fact of a past abortion is documented. However, abortion registers and medical records sometimes contain only limited additional information about the women themselves, so that studies based on them might not always be able to adjust as well as other studies can for potential confounding factors. The lack of complete information about parity and age at first birth for some women in three of the studies based on objective data (two published[9,44] and the unpublished Scottish study), and in a fourth study based on prospectively recorded self-reported data,[43] might, thus, have resulted in the relative risks in those particular studies being slightly too low. This would, however, have little effect on the overall findings, since correction for incomplete information on reproductive variables would have increased the aggregate relative risks of breast cancer from all studies with prospective information by a factor of only about 1·01, both for spontaneous and for induced abortion. Additional adjustment for socioeconomic status and for seven other potential confounding factors would also have changed the relative risk estimates only slightly.

In summary, the overall relative risks for breast cancer in the studies with prospective information—0·98 for spontaneous abortion and 0·93 for induced abortion—do not seem to be substantially biased, or to be confounded by factors known to affect risk of breast cancer. When possible, the relative risks are adjusted for parity and for age at first birth, and therefore they already allow for the extent to which having a pregnancy that ends in an abortion is affected by the previous reproductive history or affects the subsequent pattern of births. The published results for induced abortion from the studies with prospective data not included here would not have materially altered these findings, and the 99·9% confidence interval for the aggregate relative risk of breast cancer associated with induced abortion does not include values greater than 1·0. Hence, the totality of the worldwide epidemiological evidence indicates that pregnancies ending as either spontaneous or induced abortions do not have adverse effects on women's subsequent risk of developing breast cancer.

Contributors

Members of the Analysis and Writing Committee (Valerie Beral, Diana Bull, Richard Doll, Richard Peto, and Gillian Reeves) analysed data and wrote the paper, taking into account comments on earlier drafts by collaborators (listed in webappendix [http://image.thelancet.com/extras/04art2192webappendix.pdf]).

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Conflict of interest statement
None declared.

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