BREAST CANCER Prevention INSTITUTE

Abortion and Breast Cancer re: "collaborative reanalysis of data" published in *Lancet* 3/25/04[1]

The paper in *the Lancet* entitled ***"a collaborative reanalysis of data from 53 epidemiological studies, including 83,000 women with breast cancer from 16 countries"***, by Valerie Beral et al.[1], is an apparently comprehensive meta-analysis of worldwide published and unpublished data. It has been widely touted as definitive proof that there is no link between induced abortion and the risk of subsequent breast cancer (ABC link). In Beral's own words (as reported by the *Associated Press*): ***"The totality of the worldwide epidemiological evidence indicates that pregnancies ended by induced abortion do not have adverse effects on women's subsequent risk of developing breast cancer";*** and, (as reported in the *Atlanta Journal-Constitution)* ***"Scientifically, this really is a full analysis of the current data"***.

In fact, the Beral study reanalyzed the data only after a highly biased selection process which had many studies showing valid evidence of the ABC link inappropriately excluded, invalid studies whose flaws had been documented in the scientific literature inappropriately included, and valid studies whose data had been published simply not mentioned at all.

The essential features and consequences of this biased selection process are listed below:

- The claim of 53 studies is inaccurate; in fact, a total of 52 studies are included in the reanalysis.
- Since only 41 studies had been published which showed their data on induced abortion and breast cancer, it would seem that 11 studies worth of unpublished data were also included. However, since 17 published studies were either excluded or not mentioned at all, the reanalysis actually includes more unpublished studies (28 of them) than published studies (24 of them).
- Two studies were excluded for the scientifically appropriate reason that ***"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."*** Specifically, one such study from Sweden[2] in 1989 used general population statistics for comparison, instead of a control group, and one US study[3] from 1993 ascertained abortions only indirectly, by subtracting the number of children from the number of pregnancies. However, Beral et al. did not exclude three large studies which should have been excluded for the same reason. Specifically, these were:
    1. The 1997 Melbye study[4] from Denmark, in which ALL the data on legal abortions before 1973 were missing (80,000 abortions on 60,000 women),
    2. A 2001 study[5] in the UK in which over 90% of the abortions in the study population were unrecorded
    3. A 2003 Swedish study[6], in which data on all abortions after the most recent childbirth were missing. (In Sweden, where abortion is used predominantly to limit family size, that means most of the abortion records for women in the study were missing.)
- Eleven valid studies[7-17] were excluded for unscientific and inappropriate reasons, including:
    1. "***Principal investigators ... could not be traced"***
    2. ***"original data could not be retrieved by the principal investigators"***
    3. ***"researchers declined to take part in the collaboration"***
    4. ***"principal investigators judged their own information on induced abortion to be unreliable"*** (even though it had been vetted by peer review and published in a prominent medical journal).
    5. Four studies' worth of data (one on French women[18], one on Chinese women[19], One on Russian women[20], and one on African-American women[21]) were simply not even mentioned, even though they had been previously published as abstracts or included in other reviews.
- Of the 41 studies which have been previously published, 29 actually show increased risk of breast cancer among women who have chosen abortion. (Epidemiologists call this a "positive association".) 16 of these are statistically significant, which means there is at least a 95% certainty that the results cannot be explained by chance. In the Beral et al. ***"full analysis"***, 10 of the 16 significantly positive

studies in the literature were excluded for one of the unscientific reasons cited above. In all of the 15 studies Beral excluded for unscientific reasons are combined, they show an average breast cancer risk increase of 80% among women who had chosen abortion.

- The presentation of included studies is misleading. In the key figure which shows the compilation of individual studies, there is no one study that shows an overall relative risk (RR) greater than 1.41. In fact, 6 studies (two on Japanese women[7,8], two on African-American women[9,18], one on Chinese women[19] and one on Australian women[22]) have reported overall relative risks greater than 2.0 (i.e., more than a 100% risk increase with abortion. All of these were ignored or excluded as described above, except the one on Australian women, whose data were combined with several other studies and entered in the figure under the heading "Other", with a combined RR of 0.96.
- Several recent editorials and opinion pieces[23-26] on the ABC link published in scientific journals are cited in the discussion, all of which expressed the opinion that there is no ABC link. However, at least eleven recent letters[27-37] published in medical journals which have documented serious flaws in studies showing no ABC link were ignored by Beral et al.

In the Beral et al. reanalysis, the included studies were divided into two types: those which utilized prospective records to determine abortion exposure among the study population (13 studies), and those which utilized retrospective methods (interviews and/or questionnaires of breast cancer patients and control subjects; 39 studies). They demonstrated a statistically significant difference between the two types, with the average RR among the former being significantly negative (0.93), and that among the latter being significantly positive (1.11). Beral et al. then attributed this difference to the now familiar reporting bias or response bias hypothesis (see BCPI Fact Sheet on this subject). Specifically, the authors concluded that the retrospective studies' results were less reliable, ***"possibly because women who had developed breast cancer were, on average, more likely than other women to disclose previous induced abortions."*** In other words, the argument goes, retrospective studies show that a history of abortion is more common among cancer patients than among healthy women not because it really is, but just because cancer patients are more likely to admit to a history of abortion. This conclusion is invalid for four reasons:

1. It is a violation of epidemiological methodological principles to assume that a statistically significant difference alone can justify a causal interpretation (i.e., that reporting bias can be inferred simply because prospective studies, which are immune to the possibility of this particular type of bias, do not show an ABC link, while retrospective studies do).
2. Most of the data from prospective studies[4-6] included in the Beral et al. reanalysis had severe methodological flaws, for which they should have been excluded themselves (see above).
3. The study used by Beral et al. as evidence of reporting bias[38] (in fact, the only study ever published to claim direct evidence of reporting bias) has been shown to be invalid. In fact, the key piece of statistically significant evidence (i.e., that breast cancer patients had "overreported" abortions—claimed they had had abortions which had not taken place) was retracted by the authors in a published 1998 letter[39], which Beral et al. declined to cite.
4. The reporting bias hypothesis has been convincingly ruled out as an explanation for the finding of increased risk in at least four different published studies[10,15,40,41]on three continents.

In addition to compiling worldwide data on induced abortion, the Beral et al. reanalysis also included the data on spontaneous abortion (miscarriage), and found no evidence of increased risk of breast cancer in either prospective or retrospective studies. The implication is that the effect of pregnancy termination should be the same, regardless of whether it is induced or spontaneous. However, it has been well established that the reproducible epidemiological finding of no effect of spontaneous abortion is supported by a clear biological difference: Spontaneous abortions, most of the time, occur in pregnancies characterized by abnormally low levels of estrogen in the mother[42-44]. Excess exposure to estrogen, which is the main growth-promoting hormone for the breast, is implicated in both the ABC link and most other risk factors for breast cancer. Therefore, spontaneously aborting pregnancies do not subject a woman to significantly high levels of estrogen, and do not measurably increase her future breast cancer risk.

It is also very important to note that the relation of induced abortion to breast cancer is measured epidemiologically in a very artificial way. This is clear just from the title of the key figure which shows the data on induced abortion in the Beral et al. reanalysis: ***"Relative risk of breast cancer, comparing the effects of having a pregnancy that ended as an induced abortion versus effects of never having had that pregnancy."*** Obviously, a woman considering abortion is already pregnant, and does not have the option of "never having had that pregnancy". In other words, the Beral et al. study, only measures the independent, additive effect of the abortion to a woman's breast cancer risk, ignoring the fact that abortion definitely leaves a woman at a higher risk of breast cancer than would apply had she chosen to carry the pregnancy to term. As Beral et al. put it right in the opening line of the paper's introduction: ***"Pregnancies that result in a birth are known to reduce a woman's long-term risk of developing breast cancer,".*** It is therefore quite misleading to state that abortion has no effect on future breast cancer risk, even if it could be shown not to increase risk beyond the "never having had that pregnancy" level.

It is particularly telling that, for example, another risk factor which is widely acknowledged, is measured by a different standard. The case in point is combination hormone replacement therapy (HRT) for menopausal women. Menopause is a lot like full-term pregnancy, in terms of its effect on future breast cancer risk. Just as a full-term pregnancy lowers a woman's risk of breast cancer (and the younger a woman is when she has her first child, the more her future risk is lowered), the younger a woman is when she goes through menopause, the lower her risk of breast cancer. This is attributed to lower estrogen exposure due to cessation of the ovaries' production of the hormone.

When induced abortion is studied as a risk factor, women with abortion are compared (as noted above) to women who did not have a pregnancy then, rather than to women who carried the pregnancy to term. The latter comparison would show elevated risk with abortion, since post-abortive women would not have the risk-lowering effect of a full-term pregnancy.

In stark contrast, when HRT is studied as a risk factor, women taking HRT are not compared to women of the same age who did not go into menopause. Were this the case, HRT would not show up as a risk factor either, for the premenopausal women in the comparison group would not have gotten the protective effect of menopause. It would simply be concluded that HRT leaves a woman at the same risk as if she had not yet gone into menopause, and that it is not a risk factor for breast cancer.

Instead, when HRT is studied as a risk factor, premenopausal women are excluded from the analysis, (as is made explicitly clear in a major study by Beral et al. published just last year) and so postmenopausal women taking HRT are compared to postmenopausal women not taking HRT. The women in the comparison group, therefore, have gotten the protective effect of menopause. This protective effect is blocked by HRT, and so HRT shows up as a risk factor, as well it should. But abortion is judged by a different standard; one that makes it appear "safe" for women.

Finally, it is noteworthy that the authorship of the Beral et al. study is presented in a misleading way. The by-line of the paper simply says ***"Collaborative Group on Hormonal Factors in Breast Cancer*".*** This implies that the authors of all the studies included in the reanalysis are responsible, as co-authors, for the content of the paper. However, as is indicated only in a footnote at the end of the text, the "***Analysis and Writing Committee"*** consists of Valerie Beral and four co-authors, who ***"analysed data and wrote the paper, taking into account comments on earlier drafts by collaborators."*** By current internationally accepted standards of authorship, only these five people are responsible for the paper's content, and therefore qualify as authors of this paper. It also hardly seems coincidental that this group, based at the Radcliffe Infirmary of Oxford University, UK, represents a continuum of authorship dating back to 1982. This 2004 paper represents the third paper by a group with at least one common author, which papers[1,5,45] also have in common the use of inappropriate databases to draw the conclusion that induced abortion does not increase the risk of breast cancer. Unfortunately, however, it does.

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