Early Reproductive Events and Breast Cancer: A Minority Report

March 10, 2003

Introduction:

As an invited participant in the recently concluded NCI workshop "Early Reproductive Events and Breast Cancer," held Feb. 24-26, I file these public comments in the form of a minority report, inasmuch as I am in partial disagreement with the findings of the workshop submitted to the Board of Scientific Advisors and the Board of Scientific Counselors, and subsequently with the unanimous approval of these Boards, to the NCI Director, Dr. Andrew von Eschenbach.

The need for such a report as this is underscored by the fact that, although my dissent was made, in part, on the public record during the final session on Feb. 26, there was no mention of any dissent in the Summary Report which constituted the final submission of the workshop. Such an omission might indeed be misinterpreted as signifying the unanimous agreement of all the expert participants. Moreover, the fact that the workshop was abruptly concluded without prior notice at the end of what was scheduled to be the penultimate public session, there was no opportunity for anyone to make a full and formal statement enumerating and justifying any points of disagreement. Hence I take this opportunity to do so now.

II. General Comment: Scope of the workshop and opportunity for scientific scrutiny and review of the data:

1) Overall Time Constraint: The scope of the research which was presented and discussed during such a brief workshop was enormous by any measure, and thus there was little time for extensive discussion or analysis of any data. Indeed, the large number of findings that emerged testifies to the fact that, going in to the workshop, there was little if any disagreement on the vast majority of findings. For example, the breast cancer risk-lowering effect of full-term pregnancy has been so well established for so long, that in his opening address on Feb 24th, Dr. Hoover declared: "We're here to focus on the protective effect of pregnancy."
As Dr. von Eschenbach himself made clear in his opening remarks, however, the workshop was in fact prompted by controversy surrounding the question of an association between induced abortion and breast cancer incidence. Thus, while such an association has been frequently reported, the NCI had concluded-and posted on its website a year ago-that "it appears that there is no overall association…". With the workshop's having so much ground to cover, any sort of "comprehensive review", of the abortion-breast cancer data, which is what Dr. von Eschenbach envisioned, according to his opening remarks, would have been a difficult task. Nevertheless, I came to the workshop prepared to participate actively in just such an exercise.

2) Yet more troubling than the difficult time constraints for accomplishing a thorough vetting of the scientific data concerning induced abortion and breast cancer was the fact that the very design of the workshop rendered such a task impossible, to wit:

a) There were presentations only by scientists advancing the hypothesis previously advanced by the

NCI, i.e., that there is no such association. The formal presentation in the Feb. 25th public session was made by Dr. Leslie Bernstein, whose area of specialization has been mostly in other areas, namely, the effects of exercise and obesity and breast cancer risk, with no opportunity whatsoever for a balanced presentation by other authors who have published in this area. For example, I was the principal author of a comprehensive review and meta-analysis on abortion and breast cancer (Brind et al., 1996). The only other presentations on the issue were by Drs. Polly Newcomb and Mads Melbye, during the closed session of five-minute "Late-Breaking Results". It is inconceivable that a genuine and fair review of any controversial issue could ever be conducted without providing the opportunity for scientists with differing views to present and discuss their findings.

b) Abortion-breast cancer presentations included the presentation of new data (from Drs. Bernstein, Newcomb and Melbye), with no time for examination or scrutiny of such data, and,

c) Such "late-breaking" data was not made available for examination at all during the workshop. During the question and answer session following Dr. Bernstein's lecture, I specifically requested that the new data be made available for review at the workshop. However, Dr. Bernstein replied that she would not release the data until its publication. (This exchange was made on camera during a public session, the record of which will presumably be made available on the NCI website.) All new data should have been made available to workshop participants well in advance of the meeting, were there to be an opportunity for any real review.

III. Specific Dissent:

1) Contrary to the workshop finding: "Induced abortion is not associated with an increase in breast cancer risk (1)", I remain convinced that the weight of available evidence suggests a real, independent positive association between induced abortion and breast cancer risk. This conclusion is based upon:

a) The fact that of 38 epidemiological studies published through 2002, 29 have reported relative risks greater than 1.0, with 17 of these achieving at least borderline statistical significance (Among studies on US women, 13 of 15 have reported a positive overall association, 8 of them achieving at least borderline statistical significance.)

b) Cohort studies or case-control studies nested in prospective databases which do not report a positive association, are seriously flawed by massive misclassification (Melbye, et al., 1997; Goldacre et al., 2001) and/or the use of inappropriate comparison groups (Lindefors Harris et al., 1989; Melbye et al., 1997). Indeed, from what I could gather from Dr. Melbye's update of his Danish data (during the question and answer session), his stratification of relative risk by age in 1973 (date of inception of his abortion registry) was not accomplished by restricting the initial analysis to different sub-cohorts. For example, he did not reanalyze the data from scratch using only women born since 1950 (instead of 1935), thus eliminating most of the misclassified women from the analysis. Rather, he applied a statistical adjustment to the initial analysis of the entire cohort. Consequently, the large distortion of the relative risk estimate in the direction of underestimation, which we have pointed out (Brind and Chinchilli, 1997), still applies. In contrast, the only study nested in a prospective database (Howe et al., 1989) utilized a pair-matched case-control design, free of mismatching or misclassification.

c) While there remain inconsistencies in the causal hypothesis of "total estrogen exposure" as the mechanism for most risk factors (as pointed out by Dr. Hoover in his Feb. 24th address), the role of estrogen as a stimulator of cellular proliferation, as well as the known genotoxic effects of certain estrogen metabolites, still provide a biologically plausible basis for most risk factors, including

induced abortion. Bioavailable estrogen achieves its highest levels during the first two trimesters of a normal human pregnancy, inducing maximal rates of cellular proliferation.

d) Even if, for the sake of argument, one were to ignore any effect of induced abortion as an independent risk factor (i.e., as an exposure that increases risk beyond the risk level attributable to the non-pregnant state) it is grossly misleading to suggest that induced abortion has no effect on future breast cancer risk. Induced abortion has no meaning except in the case where a pregnancy is already under way. Since aborting a pregnancy denies a woman the long-term protective effect of a full-term pregnancy, it is unarguable that a woman's long-term risk of breast cancer will be greater if she chooses abortion over childbirth. Therefore, information provided to the public by the NCI, including on its website, should state this unequivocally, in order to provide meaningful guidance to women considering abortion.

2) The workshop finding: "Breast cancer risk is transiently increased after a term pregnancy.(1)" is misleading, in that it suggests that risk will be elevated beyond the level attributable to the non-pregnant state. On the contrary, although there is a transient increase, in which breast cancer risk reaches a peak approximately 5 years postpartum, this peak risk level does not exceed the risk attributable to the non-pregnant state for women under age 25 at delivery. This was acknowledged by Dr. Hsieh in the breakout session in which I participated, in agreement with what his group has reported in the literature (Lambe et al., 1994).

3) The workshop finding that the effect of preterm delivery on breast cancer risk constitutes an "epidemiologic gap"-not even suggested by level 1,2,3 or 4 evidence is not warranted, due to the presence of high quality data in the literature. Indeed, as I pointed out in my comments during the final session, the workshop paradoxically based the conclusion that induced abortion does not increase breast cancer risk largely on the work of Dr. Melbye. Yet Dr. Melbye's own group has provided excellent evidence of the risk-increasing effect of early pre-term births (before 32 weeks) using the same population database and the same statistical methodology (without the flaws in the abortion study; see Brind and Chinchilli, 2000), in agreement with the work of others (Hsieh et al., 1999). This would indicate that early premature birth has been supported by research with at least level 2 evidence. The discrepancy in the conclusions by the workshop vis-à-vis these two variables is glaring. Moreover, when I raised this concern at the final session, no one addressed it at all, notably including Dr. Melbye, who was present at the time.

Respectfully submitted,
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