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RESEARCH SYNTHESIS

Induced Abortion and Breast Cancer

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Short Version

Induced abortion is an independent risk factor for breast cancer. This document is the condensed version of a fuller assessment (see www.marri.us/abortion-breast-cancer).

Until 32 weeks' gestation, a pregnant woman will experience changes in her breast tissue that *will increase* her risk of breast cancer. Whether a pregnancy ends before 32 weeks with a premature birth, a second-trimester miscarriage,[1] or an induced abortion, a woman's risk of breast cancer is increased[2] as her natural protective processes are arrested. However, the changes that occur in the breast lobules during a pregnancy lasting more than 32 weeks offer lifelong protection against breast cancer.[3]

I. Biology of the induced abortion-breast cancer link

A. Breast development

Lobule development. A lobule is a unit of breast tissue. Type 1 and Type 2 lobules are cancer-vulnerable. Type 3 and Type 4 lobules are cancer-resistant.

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[1] Najmeh Tehranian, M. Amelbaraez, R. Salke, and S. Faghihzadeh, "The effect of abortion on the risk of breast cancer" (Iranian study presented at a conference at McMaster University, 2006). http://www.nursinglibrary.org/vhl/handle/10755/163877 (accessed April 29, 2013).

[2] L.J. Vatten, P.R. Romundstad, D. Trichopoulos, and R. Skjærven, "Pregnancy Related Protection Against Breast Cancer Depends on Length of Gestation," *British Journal of Cancer* 87 (2002): 289-290;
Mads Melbye, Jan Wohlfahrt, A.-M.N. Andersen, Tine Westergaard, and Per Kragh Andersen, "Preterm Delivery and Risk of Breast Cancer," *British Journal of Cancer* 80 (1999): 609-613.

[3] Jose Russo, Gabriela A. Balogh, Irma H. Russo, and the Fox Chase Cancer Center Hospital Network Participants, "Full-Term Pregnancy Induces a Specific Genomic Signature in the Human Breast," *Cancer Epidemiology, Biomarkers and Prevention* 17, no. 1 (January 2008): 51-66;
I. Verlinden, N. Güngör, K. Wouters, J. Janssens, J. Raus, and L. Michiels, "Parity-Induced Changes in Global Gene Expression in the Human Mammary Gland," *European Journal of Cancer Prevention* 14 (2005): 129-137.

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During the first half of pregnancy, the proliferation phase, Type 1 and Type 2 lobules increase in number. During the second half of pregnancy (after week 20), the differentiation phase, these cancer-vulnerable Type 1 and Type 2 lobules begin to mature into cancer-resistant Type 4 lobules. After 32 weeks of pregnancy, sufficient Type 4 lobules have developed that a mother is protected against breast cancer, and she incrementally gains the breast cancer risk reduction that will maximize at 40 weeks. After birth and after a mother has lactated and breastfed (or should she choose not to breastfeed), Type 4 lobules regress to Type 3 lobules, which retain the epigenetic changes that protect against cancer's development.

Table 1: Progression of Lifetime Breast Development

Breast development	**State of breast lobule development**
After puberty	75 percent Type 1 lobules and 25 percent Type 2 lobules
After conceiving	Increase in Type 1 lobules and Type 2 lobules
At 20 weeks' gestation	Absolute number of Type 1 and Type 2 lobules has greatly increased; maturation into Type 4 lobules commences
At 32 weeks' gestation	Sufficient Type 1 and Type 2 lobules have matured into Type 4 lobules that the mother has a lowered risk of breast cancer
At 40 weeks' gestation	70 to 90 percent of the breasts are cancer-resistant Type 4 lobules
After weaning	Type 4 lobules stop milk production and regress to Type 3 lobules (permanent epigenetic changes make cancer-resistant)
After menopause	Type 3 lobules change morphologically into what appear to be Type 1 lobules; however, risk reduction is maintained

If a pregnancy is healthy and lasts past 32 weeks, even should a mother deliver prematurely, she will have partial protection against breast cancer. Between 32 and 40 weeks' gestation, she will gain an additional 11 percent reduction in breast cancer risk.[4] By the end of a normal pregnancy, 70 to 90 percent of the mother's breast is composed of cancer-resistant Type 4 lobules.[5] This is why a full-term pregnancy is a known and significant protection against breast cancer.

B. Breast cancer formation

Cancer formation and breast cell growth. Cells grow through mitosis, or cell division. A resting phase follows the synthesis of new DNA and other cell structures and the subsequent cell division. Errors made when DNA is copied can be repaired during this resting phase.

Lobules' cancer vulnerability. The shorter the total cell's doubling time, the greater is the risk of forming a mutation or cancer cell, because the cell has a shorter resting

[4] L.J. Vatten, P.R. Romundstad, D. Trichopoulos, and R. Skjærven, "Pregnancy Related Protection Against Breast Cancer Depends on Length of Gestation," *British Journal of Cancer* 87 (2002): 289-290.
[5] Jose Russo and Irma H. Russo, "Development of the Human Mammary Gland," in *The Mammary Gland*, eds. M. Neville and C. Daniel (New York: Plenum Publishing Corporation, 1987).

phase, and thus less time for DNA repair. Type 1 and Type 2 lobules copy their DNA more quickly than Type 3 lobules, so they are more cancer-vulnerable. Almost all cancers arise in Type 1 (ductal cancers, 85 percent) and Type 2 (lobular cancers, 10 to 15 percent) lobules.

Estrogen and progesterone production stimulates this DNA reproduction and cell growth. Type 1 lobules have the most estrogen and progesterone receptors, Type 2 lobules have fewer than Type 1, and Type 3 lobules have negligible numbers. Differing quantities of receptors in the lobules' cells' nuclei correspond cell proliferation levels.

Cancer detection. On average, one breast cancer cell takes eight to 10 years to grow into a clinically detectable tumor mass one centimeter in diameter.[6] This is why cancer triggered by an induced abortion[7] may not become detectable for eight to 10 years.

Types of cancer. There are invasive and *in situ* cancers of both the milk ducts and milk glands. When cancer cells form but do not penetrate the basement membrane, or outer layer of the duct or gland, a cancer is said to be an *in situ* cancer. These cancers are curable, because they cannot spread to other parts of the body. Invasive cancers have penetrated the basement membrane and can spread throughout the body, becoming metastatic and life-threatening. Most invasive cancers start as *in situ* cancers.

C. Changes during pregnancy and breastfeeding

Embryo stimulation of hormone production. The embryo has a direct role in stimulating the mother's own protective biological processes. The embryo's production of hCG (human chorionic gonadotropin) acts as a chemical signal and causes the mother's ovaries to increase her production of estrogen and progesterone before the embryo is implanted in the mother's womb. These hormones sustain the pregnancy.

Benefits of early and repeated pregnancies. A woman who has her first full-term pregnancy at age 20 has a 90 percent lower risk of breast cancer than a woman who remains childless or waits until she is 30 for her first full-term pregnancy.[8] With each pregnancy after her first, a mother reduces her risk of breast cancer by 10 percent.[9] Each year a woman delays pregnancy after age 20, her risk of premenopausal breast cancer increases 5 percent and her risk of postmenopausal breast cancer increases 3

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[6] J. Gershon-Cohen, S.M. Berger, and Herbert S. Klickstein, "Roentgenography of breast cancer moderating concept of 'biologic predeterminism,'" *Cancer* 16, no. 8 (August 1963): 961-964.

[7] An examination of the timing in which breast cancer is statistically most likely to manifest itself after a woman obtains an induced abortion (around a decade to 14 years thereafter, with a seemingly diminished risk of manifestation 15 or more years after the abortion is procured) seems to indicate that induced abortion is itself a carcinogenic experience and is not merely an event that weakens a woman's defenses against breast cancer. See Appendix D of the full paper for further explanation.

[8] Mats Lambe, "Chapter Six: Reproductive Factors," in *Breast Cancer Epidemiology*, ed. Christopher I. Li (New York: Springer, 2009), 129-136.

[9] Mats Lambe, Chung-cheng Hsieh, Hsiao-wei Chan, Anders Ekbom, Dimitrios Trichopoulos, and Hans-Olov Adami, "Parity, Age at First and Last Birth, and Risk of Breast Cancer: A Population-Based Study in Sweden," *Breast Cancer Research and Treatment* 38 (1996): 305-311.

percent.[10] This results from the lengthening of the "susceptibility window," the period between menarche and a first full-term pregnancy, when the breast is composed solely of cancer-vulnerable Type 1 and Type 2 lobules and is most susceptible to carcinogenesis. A woman's breast cancer risk increases 0.7 percent for each year subsequent births are delayed after the first time she gives birth.[11]

Benefit of breastfeeding. Breast cancer risk is reduced in proportion to the length of time a mother breastfeeds. Women who exclusively breastfeed their infants will also cease their regular menstrual cycles for up to two years, which will reduce their risk of breast cancer. Many of the cycles a woman initially regains while breastfeeding are anovulatory (do not produce an egg). These cycles are lower in estrogen and do not increase the mother's risk of breast cancer as much as normal ovulatory cycles do. By contrast, a woman who lactates for the first time over 10 years after an induced abortion has a significantly increased risk of breast cancer.[12]

D. Reproductive events and breast cancer risk

First-trimester miscarriage *does not increase* breast cancer risk. In her first trimester, the mother's ovarian production of estrogen and progesterone (in response to fetal hCG) maintains the pregnancy. Early miscarriage is often a response to hormone levels insufficient to maintain the pregnancy, due to an abnormality that inhibits the embryo from producing sufficient hCG or to the mother's ovaries' failure to respond to the hCG. The levels of estrogen and progesterone during an abnormal pregnancy that result in a first-trimester miscarriage are insufficient to stimulate breast development. As the breasts were never stimulated to grow, the mother normally has no change in breast cancer risk.[13]

Second-trimester miscarriage *does increase* breast cancer risk. Second-trimester spontaneous abortions usually occur due to physical problems (e.g., the umbilical cord twisted around the fetus's neck). In such cases, estrogen and progesterone levels are normal; mothers' breasts have therefore undergone the changes that increase breast cancer risk. Because the pregnancy will not continue to term, the natural maturation process that protects the breasts will not be completed, and a mother may have an increased risk of breast cancer.

Premature delivery before 32 weeks increases breast cancer risk. If a mother's pregnancy does not continue past 32 weeks due to premature delivery, she will not get

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[10] Françoise Clavel-Chapelon and Mariette Gerber, "Reproductive Factors and Breast Cancer Risk," *Breast Cancer Research and Treatment* 72, no. 2 (2002): 107-115.

[11] Adriano Decarli, Carlo La Vecchia, Eva Negri, and Silvia Franceschi, "Age at Any Birth and Breast Cancer in Italy," *International Journal of Cancer* 67, no. 2 (July 1996): 187-189.

[12] Janet R. Daling, Kathleen E. Malone, Lynda F. Voigt, Emily White, and Noel S. Weiss, "Risk of Breast Cancer among Young Women: Relationship to Induced Abortions," *Journal of the National Cancer Institute* 86 (1994): 1584-1592.

[13] Janet R. Daling, Kathleen E. Malone, Lynda F. Voigt, Emily White, and Noel S. Weiss, "Risk of Breast Cancer among Young Women: Relationship to Induced Abortions," *Journal of the National Cancer Institute* 86 (1994): 1584-1592.

the protective effect of pregnancy against breast cancer, because her breast tissue will not have developed enough Type 4 cancer-resistant lobules.

Induced abortion increases breast cancer risk. If a woman has an induced abortion (presumably prior to 32 weeks), she has the same vulnerability as a woman delivering prematurely or experiencing spontaneous abortion not caused by low hormone levels, because her breasts will contain an increased number of Type 1 and Type 2 lobules and will not have developed sufficient cancer-resistant Type 4 lobules. The longer a woman is pregnant before an induced abortion, the more cancer-vulnerable Type 1 and Type 2 lobules she will develop.

Repeated induced abortions also increase a woman's risk of premature birth.[14] Very premature delivery may affect a woman's future breast health.

Summary. The National Cancer Institute (NCI), "the Federal Government's principal agency for cancer research and training," has concluded that induced abortion poses no increased risk of breast cancer, but this conclusion contradicts the science we have outlined above. Whether a pregnancy ends before 32 weeks with premature birth, second-trimester miscarriage, or induced abortion, a woman's risk of breast cancer is increased. The woman's breasts have been exposed to the same pregnancy hormones, more cancer-vulnerable breast tissue has formed, and this tissue's natural maturation process has been arrested. By contrast, full-term pregnancy and lactation bring most of the lobules in the breast to maturity, providing resistance to breast cancer.

II. Epidemiology of the induced abortion-breast cancer link

In our full review, we assess the results and models of some of the studies examining the induced abortion-breast cancer link from 1957 through 2013. In general, we find that while none of the studies is perfectly designed, many find a link between induced abortion and breast cancer. We address below many of the biases and problems that we detect in the studies. We also devote considerable attention to recall bias, or reporting bias, which is the primary flaw that those who deny the link between induced abortion and breast cancer assert undermines case-control studies.

A. Common biases and problems in epidemiological studies of induced abortion and breast cancer

Many design errors can skew the results of epidemiological studies. Below we list some of these biases and problems and explain how they might affect studies' results.

- **Incomplete questionnaires, low user response, and unsuitable circumstances for obtaining data:** In the Nurses Study II, the basis of the Michels study, over half of respondents did not completely answer the study's question on

[14] Brent Rooney and Byron C. Calhoun, "Induced Abortion and Risk of Later Premature Births," *Journal of American Physicians and Surgeons* 8, no. 2 (2003): 46-49.

induced and spontaneous abortion history. Rather than leaving these questions half-blank, the authors filled in the blank halves of their responses with "no." The Brauner study relied on a national survey to which over 60 percent of those invited to participate declined.

Many studies relied on interviews conducted in the home or over the telephone. Data obtained this way may be affected by some degree of reporting bias, because a respondent may be uncomfortable disclosing some information in front of a spouse or children or over the telephone. This bias may skew the study's results away from linkage of induced abortion and breast cancer.

To avoid: Studies with low response rates or in which large fractions of participants failed to complete surveys ought not to be employed as basis for analysis. Furthermore, surveys ought to be conducted in clinical settings as often as possible.

- **Health bias or survivor bias**: Women who have died of breast cancer prior to the study time cannot be accounted for, and women who have been diagnosed with breast cancer prior to the study time are often deliberately excluded from its sample. Some studies exclude women with *in situ* breast cancer.[15] This survivor or "health" bias may alter the results of the analysis concerned. It is somewhat higher in studies with representative population samples (rather than case-control studies), in studies whose populations are older (because breast cancer resulting from an induced abortion will most likely show up around a decade thereafter), and in studies that deliberately eliminate women with cancer history. (Depending on the age of the analysis, exclusion of controls with breast cancer may skew results away from or toward induced abortion-breast cancer linkage or have no effect.)

To avoid: Studies should commence with women who procure an induced abortion and track them for a minimum of eight to 10 years thereafter. This would eliminate health or survivor bias from studies. Researchers can also avoid introducing health or survivor bias, or reduce its effects, by not excluding any women who have, or who have had, invasive or *in situ* breast cancer and by limiting their analysis to women still in their

[15] *In situ* breast cancer will likely account for over 60,000 cases of breast cancer among women in 2013 in the U.S. and over 20 percent of breast cancer cases. (See American Cancer Society, "Cancer Facts & Figures 2013" [Atlanta: American Cancer Society, 2013]: 9. "An estimated 232,340 new cases of invasive breast cancer are expected to be diagnosed among women in the US during 2013; about 2,240 new cases are expected in men...In addition to invasive breast cancer, 64,640 new cases of in situ breast cancer are expected to occur among women in 2013. Of these, approximately 85% will be ductal carcinoma in situ [DCIS].") It is treated with surgery, radiation, and drugs, and it may be serious enough that a woman requires a mastectomy. Furthermore, most of these cancers develop into invasive breast cancers, though it may take 10 or more years for ductal carcinoma *in situ* to become invasive. (See Stephen P. Povoski and Sanford H. Barsky, "Chapter 10: In Situ Carcinomas of the Breast: Ductal Carcinoma in Situ and Lobular Carcinoma in Situ" in *The Breast: Comprehensive Management of Benign and Malignant Disorders*, eds. Kirby I. Bland and Edward M. Copeland III, 4th ed. (Philadelphia: Saunders Elsevier, 2009), 212: "Clearly the evidence is incontrovertible that DCIS can and often progresses to frank invasive adenocarcinoma.") Regardless: women with *in situ* cancer doubtless consider their condition to be "real" breast cancer, as do their doctors. Hence, to not account for these women is misleading.

reproductive years or just past them. Researchers should not exclude women who die of breast cancer; the relatives or friends of deceased women can be interviewed.

- **Incorrect time frames:** An individual breast cancer cell requires around eight to 10 years to grow into a clinically detectable cancer one centimeter in diameter.[16] However, some studies neglect this time frame. Some studies do not follow induced abortions for at least eight to 10 years after they are reported, and though they may eventually produce breast cancer, they do not do so in the too-brief follow-up time allotted. This skews the data away from linkage of induced abortion and breast cancer.

In analyses of the relationship between time between an induced abortion and breast cancer diagnosis, wrongly-bounded time frames may obscure induced abortion's effect.

To avoid: Studies should follow women long enough after an induced abortion—a minimum of eight to 10 years—for a resulting breast cancer to grow to a detectable size. Additionally, when studies design their analyses, their regressions' categories should be bounded so that they isolate the time frame in which a breast cancer resulting from an induced abortion is most likely to appear (e.g., zero to seven years after an induced abortion, eight to 15 years after, and 16 to 23 years).

- **Unsophisticated analysis and unsuitable comparisons:** Some analyses simply assess the influence of having any history of induced abortion on breast cancer risk Such analyses are unsophisticated, because the number of abortions a woman procures, a woman's parity status at the time she has an induced abortion, and her age and the gestational stage at which she procures the abortion determine how harmful it may be.

Additionally, incorrect reference groups[17] in analyses will obscure the influence of induced abortion on breast cancer risk. For example, the effect of induced abortion among nulliparous women will be muted if nulliparous women with induced abortions are compared to nulliparous women with no induced abortions (never-pregnant women). The breast cancer risk of never-pregnant women is greater than that of parous women; the risk associated with induced abortion will thus be muted.

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[16] J. Gershon-Cohen, S.M. Berger, and Herbert S. Klickstein, "Roentgenography of breast cancer moderating concept of 'biologic predeterminism,'" *Cancer* 16, no. 8 (August 1963): 961-964.

[17] A reference group chosen within an analysis differs from a sample's control group. For the purposes of our review, in a case-control study, controls are chosen to represent the general population, as opposed to cases. Cases and controls are divided based on whether or not they exhibit the *outcome* of interest (i.e., are you a selected breast cancer patient, or are you a member of the general population who may be healthy or who may happen to have breast cancer?).

By contrast, reference groups are the baseline for measuring the influences of different *inputs* within an analysis. For example: In an analysis of the effects of repeated abortions (input) on breast cancer risk (outcome), the group of women with zero abortions is the ideal reference group, because these women usually comprise the largest group and because they are reflective of a status quo. The health of women with one abortion, two abortions, three abortions, etc., is measured against the health of women with zero abortions: The health of women with zero abortions is the point of reference for the health of the others.

To avoid: Rather than disregarding the differences between women with different reproductive histories, advanced research should parse out their effects. Researchers ought to conduct sophisticated analyses and assess the effect of the timing of an induced abortion in a woman's reproductive life (i.e., whether the induced abortion preceded or followed a first birth, if any, and the span of time between the abortion and any subsequent first birth). Researchers also ought to assess the influences of repeated induced abortions and maternal age and gestational period at induced abortion(s).

Additionally, the standard reference group in an analysis of breast cancer risk should be composed of women who are most protected against breast cancer. In an analysis of the effects of general abortion history, the preferred reference group is women who become pregnant early in their reproductive lives, who have had no abortions or second-trimester miscarriages, and who breastfed their children. In analyses of the effects of repeated induced abortions or of maternal age or gestational period at induced abortion, parous women with zero abortions should be the reference group. Women *should not* be divided by parity status.

- **Reporting and abortion law changes:** Changes in the legality of induced abortion pose challenges for researchers and academics attempting to assess induced abortion's effect on breast cancer. If the law regulating induced abortion changed markedly during the reproductive years of a study's participants, registry data might be incomplete and respondents could be inclined not to disclose illegal abortions in interviews. The Melbye study, whose start and end dates straddled a change in the nation's abortion law, controlled for the year in which an abortion was procured and thereby controlled for liberal abortion law *and, by proxy,* controlled *out* for induced abortion. They did not report the effect that using this control had on their analysis's results. It is likely that they eliminated the effect of induced abortion on breast cancer from their results with this control.

To avoid: Studies must take into account the influence that changing induced abortion laws will have on the number of induced abortions procured and on breast cancer rates. Researchers should not control for induced abortion's legality without reporting the influence of that control.

- **Omitted variable bias:** Omitted variable bias is introduced when authors fail to fully specify (include all possible risk factors in) their model. The demonstrated importance of a given risk factor may be overinflated if a related risk factor is excluded. The models of the studies vary in their completeness, and all fail to include or to show the influence of some potential breast cancer risk factor(s) in their analyses.

To avoid: As much as possible, it is extremely important for studies to control for all potential factors for breast cancer in their analyses. Studies should avoid introducing omitted variable bias into their models by including all potential breast cancer risk factors. These factors may include the following:

Demographic factors. Age, place of residence, place of birth (urban/rural), ethnicity, marital status, occupation, household income, race, educational attainment, religion.
Parity. Ever pregnant/never pregnant, number of pregnancies, nulliparity/parity, number of full-term pregnancies, number of live births, age at first full-term pregnancy, ever had a premature birth.
Breastfeeding. Ever lactated, breastfeeding duration.
Induced abortion. Ever had an induced abortion, timing of induced abortion(s) relative to first full-term pregnancy, age at first induced abortion, number of induced abortions, gestational period (week) at induced abortions.
Spontaneous abortion. Ever had a (first-/second-trimester) spontaneous abortion, timing of (first-/second-trimester) spontaneous abortion(s) relative to first full-term pregnancy, age at first (first-/second-trimester) spontaneous abortion, number of (first-/second-trimester) spontaneous abortions, gestational period (week) at spontaneous abortions.
Menstrual cycle. Age at menarche, length of menstrual period, length of menstrual cycle, history of irregular menstruation.
Hormone use. Hormonal contraceptive use, hormonal contraceptive use before first full-term pregnancy, duration of hormonal contraceptive use, age at initiation of hormonal contraceptive use, years since initiation of hormonal contraceptive use, years since last hormonal contraceptive use, physician refusal to prescribe hormonal contraceptives, use of hormonal contraceptives for menstrual periods, estrogen/progesterone use (so-called "hormone replacement therapy" use), duration of estrogen/progesterone use.
Menopause. Menopausal status, age at menopause.
Family history. Family history of breast cancer (first- and second-degree), mutation in BRCA1 or BRCA2 gene.
Breast health and gynecological history. History of benign proliferative breast disease, history of oophorectomy, past breast biopsy, history of infertility drug use.
Other medical history. (Major) medical condition(s), occupational exposures, diabetes mellitus 2, hypertension, smoking, alcohol intake, coffee consumption, caloric intake, beta-carotene intake, body mass index (height and weight), physical activity.

- **Incomplete reporting and distinguishing between spontaneous and induced abortions:** In some studies, the data referenced fail to distinguish or to distinguish completely, whether by women's intentional misreporting or not, between spontaneous and induced abortions. Other studies fail to distinguish induced and spontaneous abortions in their general or in their more sophisticated (if any) analyses.

To avoid: Data that does not distinguish abortion types is not suitable for use. Both general and sophisticated analyses must distinguish induced and spontaneous abortion.

- **Publication bias:** The Beral meta-analysis unsystematically excluded certain datasets and baselessly dismissed results that proceeded from re-analysis of case-control studies.

To avoid: To avoid publication bias, meta-analyses and re-analyses ought not to exclude studies unsystematically. Retrospective data or re-analyses thereof should not be dismissed where they contradict prospective data *merely because* they are retrospective.

- **Insufficient sample randomization:** If a study's population is not representative (e.g., is of one socioeconomic class or race) of the general population, then the study's results are not generalizable to the general population.

To avoid: A study ought to ensure that its sample is representative of the general population. If a sample contains only urban, or white, or highly-educated women, its results are only applicable to these women.

- **Very small sample size:** If a study's sample size is too small, it may be difficult to ensure that it is sufficiently randomized, and its applicability to the general population may be limited. Furthermore, a too-small sample may inhibit the distinguishing of women around various characteristics that assessment of the relationship between induced abortion and breast cancer requires.

To avoid: Researchers ought not to use too-small samples; this will enable them to distinguish women however necessary without generating subpopulations too small for any "signal" to be perceptible over fluctuations from other sources of error.

- **No distinction between first- and second-trimester spontaneous abortions:** It is common for studies to analyze first- and second-trimester spontaneous abortions in one category, though they generally have very different causes. The failure to analyze these separately will degrade the signal of any associated breast cancer risk, so a non-significant finding is more likely to result. Furthermore, spontaneous abortions not due to hormonal insufficiencies but to physical problems may increase risk of breast cancer, and the risk conferred is indirect evidence of the effect of induced abortion.

To avoid: Studies must distinguish between the two very different types of miscarriage (first-trimester vs. second-trimester), whenever the available data makes it possible.

- **Incomplete explanation of model**: The Goldacre study compared the number of observed to expected breast cancer cases in a sample and included no explanation of how this expected number of cases had been derived.

To avoid: Researchers should not leave the reader without a clear explanation of their methods and model. Authors should note, for example, which women were included in a given category, and by what statistical means they derived their figures.

B. Epidemiological studies that deny the induced abortion-breast cancer link

Some studies deny the existence of a link between induced abortion and breast cancer (1997 Melbye,[18] 2001 Goldacre,[19] 2004 Beral,[20] 2005 Brewster,[21] 2007 Michels [the Harvard Nurses Study],[22] 2008 Henderson [California Teachers Study],[23] and 2013 Braüner[24] studies). However, careful scrutiny shows these studies were all seriously flawed. For a full review of their findings and deficiencies, see our complete paper.

C. Epidemiological and ecological epidemiological studies that affirm the induced abortion-breast cancer link

Ecological epidemiological studies use gross vital-statistic-like data, such as the incidence of breast cancer or abortions in a county, state, or country. Two ecological epidemiological studies, the 1989 Remmenick study[25] in the USSR and the 2007 Carroll study[26] in Europe, show a strong association between induced abortion and breast cancer. See our complete paper for a full review of Remmenick and Carroll's work.

At least 19 epidemiological studies, conducted across multiple countries and cultures, show a statistically significant relationship between induced abortion and breast cancer. We review three early, developmental, suggestive pieces of research (1957 Segi,[27] 1981 Pike [whose results are not statistically significant],[28] 1982 Nishiyama[29] studies), seven early epidemiological-statistical control studies (1988 Ewertz and Duffy,[30] 1989 Howe,[31]

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[18] Mads Melbye, Jan Wohlfahrt, Jørgen H. Olsen, Morten Frisch, Tine Westergaard, Karin Helweg-Larsen, and Per Kragh Andersen, "Induced Abortion and the Risk of Breast Cancer," *New England Journal of Medicine* 336, no. 2 (1997): 81-85.

[19] M.J. Goldacre, L.M. Kurina, V. Seagroatt, and D. Yeates, "Abortion and Breast Cancer: A Case-Control Record Linkage Study," *Journal of Epidemiology and Community Health* 55, no. 5 (2001): 336-337.

[20] V. Beral, D. Bull, R. Doll, R. Peto, G. Reeves, Collaborative Group on Hormonal Factors in Breast Cancer, "Breast Cancer and Abortion: Collaborative Reanalysis of Data from 53 Epidemiological Studies, Including 83,000 Women with Breast Cancer from 16 Countries," *The Lancet* 363 (2004): 1007-1016.

[21] David H. Brewster, Diane L. Stockton, Richard Dobbie, Diana Bull, and Valerie Beral, "Risk of Breast Cancer after Miscarriage or Induced Abortion: A Scottish Record Linkage Case-Control Study," *Journal of Epidemiology and Community Health* 59 (2005): 283-287.

[22] Karin B. Michels, Fei Xue, Graham A. Colditz, and Walter C. Willett, "Induced and Spontaneous Abortion and Incidence of Breast Cancer among Young Women," *Archives of Internal Medicine* 167, no.8 (2007): 814-820.

[23] Katherine DeLellis Henderson, Jane Sullivan-Halley, Peggy Reynolds, Pamela L. Horn-Ross, Christina A. Clarke, Ellen T. Chang, Susan Neuhausen, Giske Ursind, and Leslie Bernstein, "Incomplete Pregnancy Is Not Associated with Breast Cancer Risk: the California Teachers Study," *Contraception* 77 (2008): 391-396.

[24] Christina Marie Braüner, Kim Overvad, Anne Tjønneland, and Jørn Attermann, "Induced abortion and breast cancer among parous women: A Danish cohort study" [published online ahead of print April 13, 2013], *Acta Obstetricia et Gynecologica* Scandinavica 92, issue 6 (2013): 700-705.

[25] Larissa I. Remennick, "Reproductive Patterns and Cancer Incidence in Women: A Population-Based Correlation Study in the USSR," *International Journal of Epidemiology* 18, no. 3 (September 1989): 498-510.

[26] Patrick S. Carroll, "The Breast Cancer Epidemic: Modeling and Forecasts Based on Abortion and Other Risk Factors," *Journal of American Physicians and Surgeons* 12, no. 3 (2007): 72-78.

[27] M. Segi, I. Fukushima, S. Fujisaku, M. Kurihara, S. Saito, K. Asano, and M. Kamoi, "An Epidemiological Study on Cancer in Japan," *Japanese Journal of Cancer Research* (GANN) 48 (Suppl.) (1957): 1-63.

[28] M.C. Pike, B.E. Henderson, J.T. Casagrande, I. Rosario, and G.E. Gray, "Oral Contraceptive Use and Early Abortion as Risk Factors for Breast Cancer in Young Women," *British Journal of Cancer* 43, no. 1 (1981): 72-76.

[29] F. Nishiyama, "The Epidemiology of Breast Cancer in Tokushima Prefecture," *Shikoku Ichi* 38 (1982): 333-343.

[30] M. Ewertz and S.W. Duffy, "Risk of breast cancer in relation to reproductive factors in Denmark," *British Journal of Cancer* 58, no. 1 (1988): 99-104.

1993 Laing,[32] 1994 Daling,[33] 1995 Lipworth,[34] 1995 Bu,[35] 1995 Andrieu[36] studies), and 10 full, modern epidemiological studies (1999 Fioretti,[37] 2003 Becher,[38] 2006 Tehranian,[39] 2007 Naieni,[40] 2009 Dolle,[41] 2009 Xing,[42] 2009 Ozmen,[43] 2011 Khachatryan,[44] 2012 Jiang,[45] 2013 Huang[46] studies). None of these studies is perfect, but as a body, we consider the studies that affirm the induced abortion-breast cancer link superior (and their biases smaller and less fatal) to the body of studies that deny it. See our complete paper for a full review.

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[46] Yubei Huang et al., "A meta-analysis of the association between induced abortion and breast cancer risk among Chinese females," Cancer Causes and Control (2013): 1-10.

D. Recall, or reporting, bias: An assessment

The most common argument against retrospective studies affirming the abortion-breast cancer link is recall bias: the theory that cases, who have breast cancer, will be more likely to report having had abortions than (usually healthy) controls. Neither the 1991 Lindefors Harris study nor the 1996 Rookus study are sufficient evidence for this theory. The results of retrospective or case-control studies must not be dismissed out of hand. See our complete paper for a full review.

- **1991 Lindefors Harris study:** The most quoted study[47] in support of recall bias assesses Swedish data obtained through differently designed two studies: one linked induced abortion and breast cancer records and the other was a case-control study that relied on interviews. The authors compared the interview reports of abortions with the official abortion registry and found disparities, and these disparities are the basis for their argument that controls tend not to report past induced abortions.

However, their findings are an insufficient basis for this conclusion. The interviews referenced were conducted at home. Interviews conducted in participants' homes will not be comparable to those conducted in clinical environments and will be disposed to bias and underreporting (which will not likely differ between cases and controls).

Furthermore, whereas *fewer* control-procured abortions were reported in the interviews than in the registry, *more* case-procured abortions were reported in the interviews than in the registry. The authors assume that where the registry has no abortion listed for a woman and she states in her interview that she *has* procured an abortion, the registry is to be trusted over the woman herself. In their 1994 article, Daling et al.[48] state that they think it unlikely that women with no induced abortion history would claim to have had an abortion; when they recalculate under this assumption, "the size of the spurious increase in risk that arises from reporting differences between case patients and controls is only 16 [percent]" (compared to Lindefors Harris et al.'s calculated 50 percent spurious increase in risk).

[47] Britt-Marie Lindefors Harris, Gunnar Eklund, Hans-Olov Adami, and Olav Meirik, "Response bias in a case-control study: analysis utilizing comparative data concerning legal abortions from two independent Swedish studies," *American Journal of Epidemiology* 134, no. 9 (1991): 1003-1008.

[48] Janet R. Daling, Kathleen E. Malone, Lynda F. Voigt, Emily White, and Noel S. Weiss, "Risk of Breast Cancer among Young Women: Relationship to Induced Abortions," *Journal of the National Cancer Institute* 86 (1994): 1590.

Table 2: Breakdown of Induced Abortions as (un)Registered and (un)Reported in the 1991 Lindefors Harris Study

<table>
<tr><td>24 cases had abortions in the registry</td><td colspan="2">26 cases reported abortions in their interview (19 were registered, 7 were not)</td></tr>
<tr><td>5 DID NOT disclose registered abortions</td><td>19 DID disclose registered abortions</td><td>7 disclosed UNREGISTERED abortions</td></tr>
<tr><td>59 controls had abortions in the registry</td><td colspan="2">44 controls reported abortions in their interview (43 were registered, 1 was not)</td></tr>
<tr><td>16 DID NOT disclose registered abortions</td><td>43 DID disclose registered abortions</td><td>1 disclosed an UNREGISTERED abortion</td></tr>
</table>

The reader will also note here that the difference in the percentage of cases and controls underreporting their registered abortions amounts to undisclosed abortions on the part of *two or fewer cases*. (Among cases, the error in the registry is larger than the error introduced by underreporting! See the chart above.) Furthermore, when stratified, *cases* under age 40 are more likely to underreport their registered abortions than controls. Their finding that, overall, more controls underreport their abortions than cases is not robust; this small difference in underreporting is insufficient as a basis for a hypothesis used to undermine all retrospective studies in a body of literature.

- **1996 Rookus study:** The authors of this study in Holland[49] assert that one of their findings—induced abortion was found to have a large, positive, significant influence on breast cancer in the more religious southeastern areas studied and to have no significant influence on breast cancer in the less religious western areas—provides indirect evidence that reporting bias affects the results of case-control studies. However, their findings are an insufficient basis for this assertion.

The authors attribute to area religiosity the gap in the risk associated with induced abortion between the more and less religious regions, but they do not actually collect data on the religiosity of their sample. Additionally, they control (to some extent) for religiosity within their study by controlling for injectable contraceptive use—prohibited by the Roman Catholic Church—and still find an effect for induced abortion.

Recall bias is predicated on the assumption that controls are more likely to obscure induced abortion history than cases, yet 12 percent more controls than cases agreed to participate in the study (the authors state that "[a] small nonresponse study among case subjects suggested that the majority of nonresponders had not been informed of the study by their doctors and thus had not been able to consider participation").

[49] Matti A. Rookus, Flora E. van Leeuwen, "Induced Abortion and Risk for Breast Cancer: Reporting (Recall) Bias in a Dutch Case-Control Study," *Journal of the National Cancer Institute* 88, no. 23 (1996): 1759-1764.

Furthermore, the interviews in this study were conducted in the home. This would bias the study's results, completely apart from differential reporting between cases and controls or religiosity-based underreporting.

The authors did not include controls for all known breast cancer risk factors; hence, there is no need for the assertion of reporting bias as it is put forward but not substantiated by the authors. The differing risk found for induced abortion in the more religious and less religious regions may be due to any number of factors.

III. Proposed research agenda

We also suggest a research data network be built from existing breast centers, which are FDA-regulated and which are accredited by the National Accreditation Program of Breast Centers. By making the data these centers already collect comprehensive and uniform with a form that included all potential breast cancer risks, a large database for breast cancer research could be generated. The proposed network database would permit the elimination of major gaps in the literature. For a full explanation of these, see our full paper.

We have identified biases and problems that may appear in the induced abortion-breast cancer literature above. Researchers should endeavor to avoid these in their analyses.

IV. Conclusion

The independent effect of induced abortion on breast cancer risk as demonstrated in epidemiological studies varies. However, there is a general lack of controversy surrounding findings on the breast cancer risks associated with nulliparity, late age at first full-term pregnancy, early menarche, late menopause, oral contraceptive use, and hormone replacement therapy, or on the protective effect of having multiple full-term pregnancies. The increased risks posed and the protections offered by the above-noted factors all operate through the channel of hormone exposure and breast lobule maturation. As Jiang et al. assert, "[b]reast cancer is a hormone-related cancer."[50] Hence, the debate surrounding the relationship between induced abortion—another means of exposure to high hormonal levels but not mitigated by cell differentiation—and breast cancer is incongruous with the low level of debate surrounding many other risks or protections.

We have attempted to provide a comprehensive review of the biology and epidemiology of the induced abortion-breast cancer link. We hope we have mapped out a way forward that those in the medical and academic community will find appealing.

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[50] A.R. Jiang, C.M. Gao, J.H. Ding, S.P. Li, Y.T. Liu, H.X. Cao, J.Z. Wu, J.H. Tang, Y. Qian, and K. Tajima, "Abortions and Breast Cancer Risk in Premenopausal and Postmenopausal Women in Jiangsu Province of China," *Asian Pacific Journal of Cancer Prevention* 13 (2012): 35. http://www.apjcpcontrol.org/page/popup_paper_file_view.php?pno=MzMtMzUgMTIuMiZrY29kZT0yNzAxJmZubz0w&pgubun=i (accessed December 7, 2012).