
Breast Cancer and Induced Abortion: A Comprehensive Review of Breast Development and Pathophysiology, the Epidemiologic Literature, and Proposal for Creation of Databanks to Elucidate All Breast Cancer Risk Factors

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ABSTRACT: This article synthesizes breast developmental biology and pathophysiology which cause induced abortion to be a risk for breast cancer with the extant epidemiologic studies that differentiate induced and spontaneous abortions. These studies are rigorously statistically analyzed. It also outlines a proposal for the establishment of much-needed data banks that will be able to supply gold-standard prospective data for all breast cancer risks. We recommend collecting longitudinal data through the use of National Accreditation Program for Breast Centers (NAPBC)-approved mammography centers, which can also be linked to a corresponding tissue bank. The data is greatly needed to control the cost of mass mammography screening by identifying those women who are at higher risk of breast cancer and in need of regular or early screening. It is the authors' hope that through this rigorously referenced review, analysis, and proposal that medical science will be advanced and both medical professionals and the lay public will understand the risks contributing to the continued epidemic of breast cancer both here and abroad.

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I. Introduction: Induced Abortion Increases Breast Cancer Risk.

In the past 30 years, landmark advances in developmental and molecular breast biology coupled with multiple epidemiologic studies from around the world have shown induced abortion to be an independent risk factor for breast cancer. Induced abortion before 32 weeks' gestation will impede the natural maturation process in the breast such that there is a significantly greater probability that breast cancer will develop later. Those most at risk of developing breast cancer after an abortion include teenagers (almost half of all first induced abortions between 2006 and 2010 were reportedly to teenagers¹) and women over 30, especially if they have a family history of breast cancer.²

A 2013 study published in the *Journal of the American Medical Association*³ found an alarming increase in "distant" breast cancer among women aged 25 to 39. "Distant" breast cancer is breast cancer that has metastasized "remote[ly]... ([to the] bone, brain, lung, etc)."⁴ This rise in breast cancer incidence amounted to an increase of 2 percent per year from 1976 to 2009,⁵ and it persisted across three different sets of National Cancer Institute data.⁶

A review of National Cancer Institute cancer data⁷ shows invasive breast cancer incidence was 24 percent higher in 2007 than in 1976. At its peak over that period, in 1999, invasive breast cancer incidence was almost 40 percent higher than in 1976. These data show an increase of over 400 percent in *in situ* breast cancer incidence among women under age 50 between 1976 and 2007. An approximately 560 percent increase in *in situ* breast cancer incidence occurred among women of all ages over the same period.

¹ Marriage and Religion Research Institute, *Demographics of Women Who Have Had an Abortion: from the National Survey of Family Growth 2006-2010*, by Patrick Fagan and Scott Talkington (2013): 8. www.marri.us/abortion-demographics (accessed August 7, 2013). Note that teenagers procured about 18 percent of all induced abortions in 2008. Guttmacher Institute, *Characteristics of U.S. Abortion Patients, 2008*, by Rachel K. Jones, Lawrence B. Finer, and Susheela Singh, 2010.

² 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.

³ Rebecca H. Johnson, Franklin L. Chien, and Archie Bleyer, "Incidence of Breast Cancer With Distant Involvement among Women in the United States, 1976 to 2009," *Journal of the American Medical Association* 309, no. 8 (2013): 800-805.

⁴ *Id.* at 800.

⁵ When broken down, women aged 25 to 34 were found to have a slightly larger annual percent increase in risk than women aged 35 to 39. Among women aged 25 to 39, the increased risk was significant and pronounced among black women, as well as among non-Hispanic white women and women residing in metropolitan areas, though fewer years of data were available for this analysis.

⁶ SEER (the program that collected the referenced data), or the Surveillance, Epidemiology, and End Results Program, is a program of the National Cancer Institute.

⁷ National Cancer Institute, *SEER Cancer Statistics Review, 1975-2007*, by S.F. Altekruse, C.L. Kosary, M. Krapcho, N. Neyman, R. Aminou, W. Waldron, J. Ruhl, N. Howlander, Z. Tatalovich, H. Cho, A. Mariotto, M.P. Eisner, D.R. Lewis, K. Cronin, H.S. Chen, E.J. Feuer, D.G. Stinchcomb, and B.K. Edwards (eds.), Bethesda, MD. Based on November 2009 SEER data submission, posted to the SEER web site, 2010; http://seer.cancer.gov/csr/1975_2007/ (accessed September 9, 2009), See Tables 4.7 and 4.8.

The study published in the *Journal of the American Medical Association* makes little attempt to empirically determine the source of this increase in breast cancer incidence among younger women. However, that the increase is occurring is reason enough to study more carefully the increased vulnerability to breast cancer that we think induced abortion confers on women.

Given what is known of breast physiology and the reproductive risks described in standard medical texts,⁸ it is most natural that induced abortions would cause an increase in the risk of breast cancer. It has been known for centuries that remaining childless increases a woman's risk for breast cancer; conversely, it has also been known that pregnancy is protective. In 1743, Ramazzini of Padua observed that there was a higher incidence of breast cancer among nuns.⁹ Nuns were largely childless, whereas the rest of the population had pregnancies early in their reproductive lives.

No matter the length of her pregnancy (save those that end in first-trimester spontaneous abortions¹⁰), until 32 weeks' gestation, a woman will experience changes in her breast tissue that *will increase* her risk of breast cancer. However, the epigenetic changes that occur in the breast lobules during a pregnancy lasting more than 32 weeks offer lifelong protection against breast cancer.¹¹ Molecular biologists have determined that progenitor cells, or stem cells, in the breast do not become terminally differentiated (reach their full potential growth, or mature) until they have undergone pregnancy and have lactated.¹² It has also been determined that these progenitor cells are lower in number in parous women and the number of these cells is related to breast cancer risk.¹³ It is only after 32 weeks' gestation that elevated levels of pregnancy hormones allow sufficient maturation of cancer-resistant breast tissue to occur. Therefore, whether a pregnancy ends before 32 weeks with a premature birth, a second-trimester spon-

⁸ Rena Kass, Anne T. Mancino, Arlan L. Rosenbloom, V. Suzanne Klimberg, and Kirby I. Bland, Chapter 3: "Breast Physiology: Normal and Abnormal Development and Function," and Victor G. Vogel, Chapter 16: "Epidemiology of Breast Cancer," in *The Breast: Comprehensive Management of Benign and Malignant Disease*, eds. Kirby I. Bland and Edward M. Copeland III, 3rd ed. (Philadelphia: Saunders, 2003), 43-63, 341-354.

⁹ Bernardino Ramazzini with J. Corona, *De morbis artificum diatriba* (Venice, 1743), as cited in Mats Lambe, "Reproductive Factors," in *Breast Cancer Epidemiology*, ed. Christopher E. Li (Springer, 2009), 120.

¹⁰ As developed later in the article, women who have a spontaneous abortion (miscarriage) in their first trimester are unlikely to have had the breast tissue change associated with a normal pregnancy.

¹¹ 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. Gungör, 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.

¹² Werner Boecker, Stefanie Weigel, Walter Heindel, and Petra Stute, "The Normal Breast," in *Pre-neoplasia of the Breast: A New Conceptual Approach to Proliferative Breast Disease*, ed. W. Boecker (Munich: Elsevier Saunders, 2006), 1-28.

¹³ S. Choudhury et al., "Molecular Profiling of Human Mammary Gland Links Breast Cancer Risk to a p27(+) Cell Population with Progenitor Characteristics," *Cell Stem Cell* 13 (2013): 117-130.

taneous abortion (that is, a miscarriage),¹⁴ or an induced abortion, a woman's risk of breast cancer is increased.¹⁵

After a full-term pregnancy, only about 10 to 30 percent of a mother's breast tissue remains susceptible to forming cancer.¹⁶ With each pregnancy a woman has subsequent to her first, her risk of breast cancer will decrease another 10 percent.¹⁷ However, the longer a woman waits to have her first full-term pregnancy, the higher is her risk of breast cancer, as her immature, cancer-vulnerable breast tissue is exposed to carcinogens for a longer duration. This period of time between menarche (the first menstrual cycle) and a pregnancy is termed the "susceptibility window," as the breast is most adversely affected by carcinogens during that period.¹⁸ A long susceptibility window accounts for the transient (but statistically significant) rise in breast cancer risk that occurs in women who delay their first pregnancy until after age 30.¹⁹ During her susceptibility window, a woman may have developed a mutation or a cancer cell that the proliferation phase of her pregnancy would cause to grow.

Hence, a woman who is pregnant and chooses abortion to end her pregnancy will deny herself the risk-lowering effects of a full-term pregnancy and will either remain childless or delay pregnancy, both of which increase her risk of premenopausal breast cancer at a rate of 5 percent per year of delay.²⁰ These also put her at risk of premature

¹⁴ 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).

¹⁵ 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.

¹⁶ J. Russo, Y.-F. Hu, X. Yang, and I. Russo, Chapter 1: "Developmental, Cellular, and Molecular Basis of Human Breast Cancer," *Journal of the National Cancer Institute Monographs* 27 (2000): 22. See also 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).

¹⁷ Mats Lambe, Chung-cheng Hsieh, Hsiao-wei Chan, Anders Ekblom, 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.

¹⁸ F.M. Biro and M.S. Wolff, Chapter 2: "Puberty as a Window of Susceptibility," in *Environment and Breast Cancer*, ed. J. Russo (New York: Springer, 2011), 29-36.

¹⁹ Note that women who delay first birth until age 25 or later have, relative to nulliparous women, a marginally statistically significantly increased risk of diagnosis at age 30. See Mats Lambe, Chung-cheng Hsieh, Dimitrios Trichopoulos, Anders Ekblom, Maria Pavia, and Hans-Olov Adami, "Transient increase in the risk of breast cancer after giving birth," *New England Journal of Medicine* 331 (1994): 5-9.

²⁰ Françoise Clavel-Chapelon and Mariette Gerber, "Reproductive Factors and Breast Cancer Risk," *Breast Cancer Research and Treatment* 72, no. 2 (2002): 107-115.

delivery before 32 weeks,²¹ which would double her breast cancer risk.²² However, abortion itself poses an independent risk of breast cancer; that risk is the subject of this review.

We have endeavored to make the present review comprehensive. We have drawn on the literature and relevant medical texts to explain breast physiology and the epidemiologic studies that differentiate induced from spontaneous abortion in its relation to breast cancer, and we make recommendations for further research.

What follows immediately is a review of the biological changes in breast tissue over a woman's lifetime and during pregnancy. Thereafter, we review and critique the research available and its evaluation by academics and relevant scientific organizations. We then review various guidelines for establishing causation in epidemiological studies and conclude with research recommendations.

II. Developmental Biology Affirms the Induced Abortion-Breast Cancer Link.

In the sections to follow, we will address the development of the breast over the lifetime, the development of breast cancer, and the changes that arise in the breast during pregnancy and lactation. We also discuss the occurrence of miscarriage, premature delivery, induced abortion, and full-term pregnancy, and the risk of or protection against breast cancer that these reproductive events provide. As we show, the developmental biology of changes in the breast that occur during puberty and during a normal pregnancy supports the existence of an independent link between induced abortion and breast cancer.

A. Breast Development

Lobule growth

An infant is born with immature alveolar buds and Type 1 lobules under the nipple-areola complex. (A lobule is a unit of breast tissue comprised of a milk duct with surrounding mammary [milk] glands, which are both composed of individual breast cells.) After puberty, females will develop more Type 1 lobules. Some Type 1 lobules will become Type 2 lobules after puberty as the breasts enlarge, at which point the breast contains a mixture of approximately 75 percent Type 1 lobules and 25 percent Type 2 lobules. Type 1 and Type 2 lobules are vulnerable to cancer.

²¹ P. Shah and J. Zao, on behalf of Knowledge Synthesis Group of Determinants of Preterm/LBW Births, "Induced Termination of Pregnancy and Low Birthweight and Preterm Birth: A Systematic Review and Meta-Analyses," *British Journal of Obstetrics and Gynaecology* 116, no. 11 (2009): 1425-1442; Hanes M. Swingle, Tarah T. Colaizy, M. Bridget Zimmerman, and Frank H. Morriss, "Abortion and Risk of Subsequent Preterm Birth: A Systematic Review and Meta-Analyses," *Journal of Reproductive Medicine* 54 (2009): 95-108.

²² 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; C.C. Hsieh, J. Wu, M. Lambe, D. Trichopoulos, H.O. Adami, and A. Ekblom, "Delivery of Premature Newborns and Maternal Breast Cancer Risk," *The Lancet* 353 (1999): 1239.

During the first half of pregnancy, the proliferation phase, Type 1 and Type 2 lobules increase in number. By week 20 of a 40-week (full-term) pregnancy, the breast has doubled in volume. The number of lobules in the breast increase through a decrease in the amount of breast stroma, or connective tissue, around the lobules.

During the second half of pregnancy (after week 20), the differentiation phase, these immature, *cancer-vulnerable* Type 1 and Type 2 lobules begin to mature into cancer-resistant Type 4 lobules. Type 4 lobules are capable of producing the milk, or colostrum, the baby will need. After 32 weeks of pregnancy, sufficient Type 4 lobules have developed that a mother is protected against breast cancer, and she begins to incrementally gain the benefit of risk reduction that will maximize at 40 weeks. *By the end of a normal pregnancy, 70 to 90 percent of the mother's breast is composed of cancer-resistant Type 4 lobules.*

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 the development of cancer. This epigenetic change involves the "down-regulation" or "switching off" of lobule reproduction DNA, which thereafter stays permanently switched off and thereby protects against cancer.²³ *A woman's risk of breast cancer will decrease an additional 10 percent with each subsequent pregnancy.*²⁴ This observed additional reduction in risk may be due to increased breastfeeding among these women, fewer lifetime menstrual cycles, and more anovulatory postpartum cycles (that is, postpartum cycles that do not produce an egg) with lower estrogen exposure, all known to reduce risk. Therefore, the woman who has a full-term pregnancy obtains lifelong benefits from the epigenetic changes it produces in the breast cells and gains even more risk reduction with additional births and breastfeeding.²⁵

After menopause, Type 3 lobules morph into what appear to be Type 1 lobules microscopically; however, the epigenetic changes which have afforded cancer resistance remain.

²³A "down-regulated" gene is turned off; an "up-regulated" gene is turned on. A human's cells all contain the same DNA. Turning different genes on or off (epigenetics) produces different kinds of cells. (For example: A liver cell and a skin cell contain the same DNA, but different genes in each cell are up-regulated and down-regulated, which is why some cells are liver cells and others are skin cells.)

²⁴Mats 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.

²⁵V. Beral, D. Bull, R. Doll, R. Peto, G. Reeves, Collaborative Group on Hormonal Factors in Breast Cancer, "Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50,302 women with breast cancer and 96,973 women without the disease," *The Lancet* 360 (2002):187-195.

Figure 1: Lobule Development before, during, and after Pregnancy

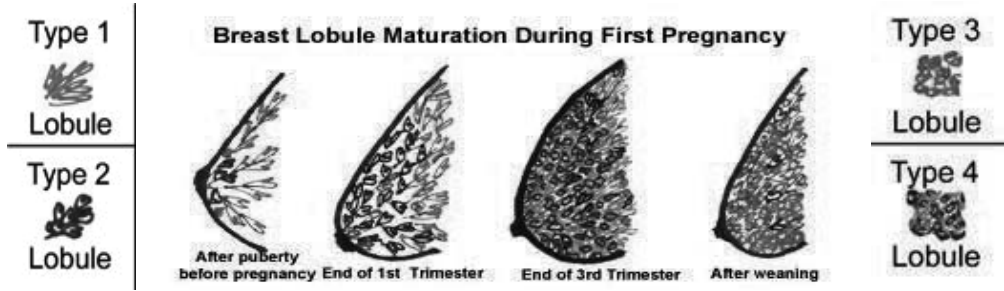


Table 1: Progression of Lifetime Breast Development²⁶

Breast development	State of breast lobule development
After puberty	75 percent Type 1 and 25 percent Type 2 lobules
After conceiving	Increase in Type 1 and Type 2 lobules
At 20 weeks' gestation	Absolute number of Type 1 and Type 2 lobules has greatly increased while stromal ²⁷ breast tissue has decreased as the breast has doubled in volume; 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, which have permanent epigenetic changes that protect against cancer
After menopause	Type 3 lobules change morphologically into what appear to be Type 1 lobules; however, their genes do not change in their up- or down-regulation, so risk reduction is maintained

Lobular structure

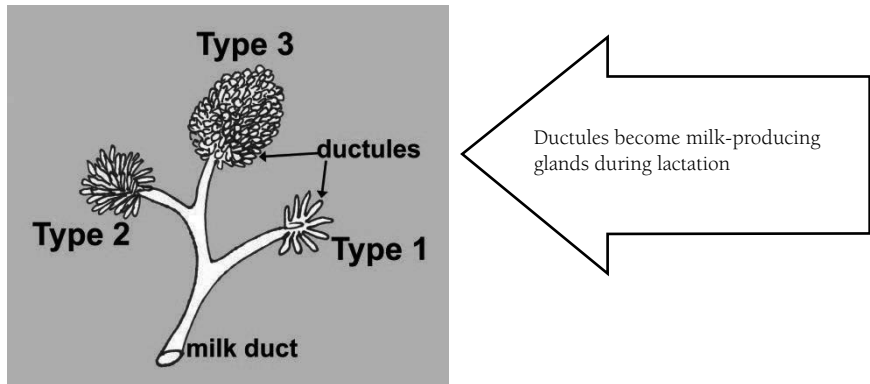
Again, a lobule is a unit of breast tissue comprised of a milk duct with surrounding mammary (milk) glands, which are both composed of individual breast cells.

²⁶ J. Russo, Y.-F. Hu, X. Yang, and I. Russo, Chapter 1: “Developmental, Cellular, and Molecular Basis of Human Breast Cancer,” *Journal of the National Cancer Institute Monographs* 27 (2000): 17-37; 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).

²⁷ Stroma is the tissue of the breast that is neither milk ducts nor glands.

The ductules which surround the terminal end, or milk duct, become the glands where milk is produced.²⁸ Each type of lobule has varying numbers of ductules, which become the milk-producing glands during lactation. These lobules are different morphologically (i.e., in their shape) as well as metabolically (e.g., in their doubling time).

Figure 2: Lobule Types and their Structures



Lobular hormone sensitivity

Type 1 lobules have a greater number of estrogen and progesterone receptors in their cells' nuclei than Type 2 lobules do. Type 2 lobules have significantly more of these receptors than Type 3 lobules. Stimulation of these estrogen and progesterone receptors causes breast cell growth through mitosis (cell division). The more receptors a breast cell has, the more sensitive and reactive it is to hormone levels. Pregnancy (as well as monthly menstrual cycles), which is characterized by elevated estrogen and progesterone levels, causes breast growth.

As stated above, the breast doubles in volume by 20 weeks of pregnancy by reducing the amount of connective tissue (stroma) and increasing the numbers of lobules it contains.²⁹ By 32 weeks, full differentiation to more cancer-resistant Type 4 lobules, capable of producing colostrum, has occurred in sufficient numbers that the breast is protected against cancer.³⁰

All these structural and metabolic changes are regulated by genes turning on and off (epigenetic switches). We know which genes have been "turned off" and "turned

²⁸ The ductules come off the duct draining the lobule called the "terminal end duct." The small terminal ducts drain into larger and larger milk ducts, or lactiferous ducts. These lactiferous ducts transport milk to the lactiferous sinuses, which are just below the nipple.

²⁹ This is the result of hCG stimulation of estrogen and progesterone production in the first half of pregnancy, which, in turn, stimulates breast cell division.

³⁰ The mother's hPL levels rise three times higher than her prolactin levels by the end of pregnancy, which enables full differentiation to Type 4 lobules.

on” (down-regulated and up-regulated) throughout a full term of pregnancy³¹ under the influence of pregnancy hormones.

Concurrent fetal development

During this time of maternal breast maturation, a parallel development is occurring in the fetus. During the fourth week of pregnancy, the milk streak (area of future breast tissue development) of the embryo forms. Development of the mammary ridge follows in the fifth week, and invasion into the chest wall takes place between the seventh and eighth weeks. (In humans, only two areas of the milk ridge persist in forming breasts.) The solid cords of epithelial cells in the fetal chest wall become canalicularized, or hollow, at 32 weeks, thereby developing the milk ducts and glands of the newly forming fetal breasts.³²

B. Breast Cancer Formation

Cancer formation and breast cell growth

Cells grow through mitosis, or cell division. Before a single cell divides into two cells, it must make a complete copy of its DNA. The process of cell division occurs during the cell cycle, which also includes a resting phase after the synthesis of new DNA and other cell structures; thus, if errors are made when DNA is copied, they can be repaired during this resting phase.

Table 2: Lobular Morphology, Cancer Vulnerability, and Structure

Type of lobule	Morphology of lobules	Type of cancer that forms from lobules	Structural and metabolic differences of lobules
Type 1	Average 11 ductules per lobular unit	Ductal cancers (which are approximately 85 percent of all breast cancers), arising in milk ducts ³³	<ul style="list-style-type: none"> • Highest number of estrogen and progesterone receptors in the cells • Highest rate of cell proliferation (marked by Ki67 protein) • Shortest DNA doubling time

³¹ 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. Gungör, 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.

³² 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).

³³ A lobule has a milk duct and glands. The gland makes the milk, and the milk duct collects the milk. Under the microscope, pathologists can determine whether cancer is ductal or lobular carcinoma. Ductal cancers start in the ducts of Type 1 lobules and lobular cancer start in the glands of Type 2 lobules.

Type 2	Average 47 ductules per lobular unit	Lobular cancers (which are approximately 15 percent of all breast cancers), arising in milk glands	<ul style="list-style-type: none"> • Approximately half the number of estrogen and progesterone receptors as Type 1 lobules • One third of the cell proliferation marker Ki67 protein of Type 1 lobules • A shorter DNA doubling time than Type 3 lobules
Type 3	Average 81 ductules per lobular unit	Cancer-resistant	<ul style="list-style-type: none"> • Negligible numbers of estrogen and progesterone receptors • Less than one tenth of the cell proliferation marker Ki67 protein of Type 1 and Type 2 lobules • Type 4 lobules regress to Type 3 after cessation of breastfeeding
Type 4	Average 81 ductules per lobular unit	Cancer-resistant	<ul style="list-style-type: none"> • Absence of proliferation³⁴ • Lobules produce and contain colostrum (early milk) or mature milk in their glands

Cancer formation

The time that mitosis (splitting from one into two cells) and DNA synthesis take is the cell's doubling time. The cells of each type of lobule have different doubling times and other measures of metabolic activity, such as cellular proliferation (identified by the level of the Ki67 protein it contains).³⁵ A short doubling time may result in more mutations, because the cell has a shorter resting phase (i.e., a shorter time for DNA repair). Cancer develops from a mutation or damage done to a cell's DNA.

Genotoxins (such as radiation or some chemicals) can directly damage DNA and cause a mutation without cell division. Unless the mutation occurs in a critical gene (such as p53, a tumor suppressor gene which normally detects mutations in DNA at the G1 checkpoint, and in which a mutation permits many cancer-producing mutations to

³⁴ Type 4 lobules do not proliferate, as they are terminally differentiated and producing milk.

³⁵ R. Dickson and J. Russo, Chapter 2: "Biochemical Control of Breast Development," in *Diseases of the Breast*, eds. Jay R. Harris, Marc E. Lippman, Monica Morrow, and C. Kent Osborne, 2nd ed. (Philadelphia: Lippincott Williams & Wilkens, 2000), 16-18.

pass the G1 checkpoint unchanged), most cancers form after several mutations have built up in a cell over a number of years. After mitosis, any mutated daughter cells will undergo mitosis again with a greater chance of more mutations forming.

Lobules' cancer vulnerability

The shorter the time in which the DNA doubles, or copies itself, the greater is the risk of forming a mutation or cancer cell. Type 1 and Type 2 lobules copy their DNA more quickly than Type 3 lobules, so they are more cancer-vulnerable. Again, when DNA is copied quickly and the cell cycle is shorter, there is less time in the resting phase (when DNA mistakes are repaired), so more mutations are passed on. There is not enough time to repair all of them before the cell divides.

Eighty-five percent of breast cancers arise in Type 1 lobules (ductal cancers). Ten to 15 percent of all breast cancers arise in Type 2 lobules (lobular cancers). Almost all cancers arise in Type 1 and Type 2 lobules.

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

Cancer detection

A breast cell's doubling time accounts for the time a tumor takes to become large enough to be clinically detectable through an imaging study, such as a mammogram, or by a physical exam through palpation, or feeling the breast. On average, one microscopic breast cancer cell takes eight to 10 years to grow through mitosis into a tumor mass (lump) one centimeter in diameter.³⁶ This is why cancer caused by an induced abortion³⁷ 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. This classification depends upon the origin and location of the cancer cells. The receptors of the cancer cells are also examined and reflect their genetic phenotype.

When cancer cells form in the milk ducts or glands but do not penetrate the outer layer of the duct or gland (the basement membrane), a cancer is said to be an *in situ* cancer. Less than half of these ductal *in situ* cancers can be felt as a "lump," but 90 percent

³⁶ 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.

³⁷ 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 E for further explanation.

are detected by mammographic calcifications.³⁸ These cancers are curable, because they have not penetrated the basement membrane where the lymphatic channels or blood vessels are located; they cannot spread to other parts of the body. *In situ* cancers can develop in the milk duct and form ductal carcinomas *in situ*. They may also arise in the milk glands and form lobular carcinomas *in situ*.

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, and most (85 percent) of these are ductal cancers.

Breast cancer treatment has become more effective by routinely analyzing the cancer cells for estrogen (ER), progesterone (PR), and Her 2 neu (HER2) receptors. These receptors can be positive (+) or negative (-). They are also assessed by how proliferative the cells are by measuring the protein Ki67.

Breast cancers are sometimes described by the array of genes that are expressed. At present there are four major subtypes: luminal A (ER+ and/or PR+, HER2-, low Ki67), luminal B (ER+ and/or PR+, HER2+ or HER2- with high Ki67), triple-negative/basal-like (ER-, PR-, HER2-), and HER2 type (ER-, PR-, HER2+).

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. A mother's breasts enlarge very soon after conception, becoming sore and tender, one of the first signs of pregnancy. This occurs because 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 even implanted in the mother's womb. (During the first half of pregnancy, estrogen levels rise rapidly: 2,000 percent during the first trimester.) These hormones sustain the pregnancy. Again, the maturation process that protects a woman from breast cancer happens only because the fetal placental unit produces the hormones hCG and hPL (human placental lactogen), which prepare the mother to breastfeed. HCG also protects the mother from forming breast cancer by stimulating the mother's production of alpha inhibin, which is a tumor suppressor protein.³⁹ Research shows hCG can inhibit breast cancers from forming.⁴⁰

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

³⁸ Harold J. Burstein, Kornelia Polyak, Julia S. Wong, Susan C. Lester, and Carolyn M. Kaelin, "Ductal Carcinoma in Situ of the Breast," *New England Journal of Medicine* 350 (2004): 1430-1441.

³⁹ Irma H. Russo, M. Koszalka, and Jose Russo, "Effect of human chorionic gonadotropin on mammary differentiation and carcinogenesis," *Carcinogenesis* 11 (1990): 1849-1855.

⁴⁰ Irma H. Russo and Jose Russo, "Pregnancy-induced changes in breast cancer risk," *Journal of Mammary Gland Biology and Neoplasia* 16, no. 3 (September 2011): 221-233.

her first full-term pregnancy.⁴¹ 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 percent.⁴² This results from the lengthening of the “susceptibility window,” the period between menarche and a first full-term pregnancy, when the breast is most susceptible to carcinogenesis. It is the time when the breast is composed solely of cancer-vulnerable Type 1 and Type 2 lobules. However, if a woman delays her first pregnancy until after age 30, she will have a transiently (but statistically significantly) increased risk of breast cancer for 10 to 15 years before she gains the risk-lowering benefit of pregnancy.⁴³

Furthermore, a woman’s breast cancer risk increases 0.7 percent for each year subsequent births are delayed after the first time she gives birth.⁴⁴ However, as stated earlier, with each pregnancy after her first, a mother reduces her risk of breast cancer by 10 percent.⁴⁵

Benefit of full-term pregnancy before an induced abortion

Full-term pregnancy is protective against breast cancer; hence, it would seem that a woman who procures an induced abortion only after she has given birth is at a lower risk of breast cancer than a woman who has an induced abortion before giving birth.⁴⁶

China’s one-child policy means that many women obtain abortions after the birth of their first child. Chinese women (as is the case for all women) who have their first abortion after they have already had a full-term pregnancy have a lower risk of breast cancer than those who have not already had a full-term pregnancy when they obtain an abortion.⁴⁷

⁴¹ Mats Lambe, “Chapter Six: Reproductive Factors,” in *Breast Cancer Epidemiology*, ed. Christopher I. Li (New York: Springer, 2009), 129-136.

⁴² Françoise Clavel-Chapelon and Mariette Gerber, “Reproductive Factors and Breast Cancer Risk,” *Breast Cancer Research and Treatment* 72, no. 2 (2002): 107-115.

⁴³ Note that women who delay first birth until age 25 or later have, relative to nulliparous women, a marginally statistically significantly increased risk of diagnosis at age 30. See Mats Lambe, Chung-cheng Hsieh, Dimitrios Trichopoulos, Anders Ekblom, Maria Pavia, and Hans-Olov Adami, “Transient increase in the risk of breast cancer after giving birth,” *New England Journal of Medicine* 331 (1994): 5-9.

⁴⁴ 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.

⁴⁵ Mats Lambe, Chung-cheng Hsieh, Hsiao-wei Chan, Anders Ekblom, 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.

⁴⁶ Loren Lipworth, Klea Katsouyanni, Anders Ekblom, Karin B. Michels, and Dimitrios Trichopoulos, “Abortion and the Risk of Breast Cancer: A Case-Control Study in Greece,” *International Journal of Cancer* 61 (1995): 183; see also 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): 1762.

⁴⁷ See Z. Ye, D.L. Gao, Q. Qin, R.M. Ray, and D.B. Thomas, “Breast cancer in relation to induced abortions in a cohort of Chinese women,” *British Journal of Cancer* 87, no. 9 (2002): 976. The Ye study stated that, among the cancer patients studied, only 12 women had undergone an abortion *before* their first child’s birth and 320 had procured an abortion *after* their first child’s birth.

Benefit of breastfeeding

Many studies have shown⁴⁸ that breast cancer risk is reduced in proportion to the length of time a mother breastfeeds, should she choose to do so. Women who breastfeed such that all of their infant's calories come from their breast milk will also cease their regular menstrual cycles for up to two years. The fewer menstrual cycles a woman has in her lifetime, the lower is her risk of breast cancer. Many of the cycles a woman initially regains while breastfeeding are anovulatory (that is, an egg is not produced). These anovulatory cycles are lower in estrogen and therefore do not increase the mother's risk of breast cancer as much as normal ovulatory cycles do.

Daling et al. found no detectable increased risk for women who first lactate fewer than ten years after an induced abortion, relative to women with no induced abortion history. 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.⁴⁹

D. Miscarriage, Premature Delivery, and Breast Cancer Risk

First-trimester miscarriage does not increase breast cancer risk.

Thirty-one percent of all conceptions will end in a miscarriage.⁵⁰ Over 90 percent of miscarriages take place in the first trimester.⁵¹

⁴⁸ Collaborative Group on Hormonal Factors in Breast Cancer, "Breast cancer and breastfeeding: collaborative reanalysis of individual data from 47 epidemiological studies in 30 countries, including 50,302 women with breast cancer and 96,973 women without the disease," *Lancet* 360 (2002): 187-195; P.A. Newcomb, B.E. Storer, M.P. Longnecker, et al., "Lactation and a reduced risk of premenopausal breast cancer," *New England Journal of Medicine* 330 (1994): 81-87; I. Romieu, M. Hernandez-Avila, E. Lozano, et al., "Breast cancer and lactation history in Mexican women," *American Journal of Epidemiology* 143 (1996): 543-552; H. Becher, S. Schmidt, and J. Chang-Claude, "Reproductive factors and familial predisposition for breast cancer by age 50 years. A case-control-family study for assessing main effects and possible gene-environment interaction," *International Journal of Epidemiology* 32 (2003): 38-50; Kourosh Holakouie Naieni, Ali Ardalani, Mahmood Mahmoodi, Abbas Motevalian, Yoosef Yahyapoor, and Bahareh Yazdizadeh, "Risk Factors of Breast Cancer in North of Iran: A Case-Control in Mazandaran Province," *Asian Pacific Journal of Cancer Prevention* 8 (2007): 395-398; http://www.apocp.org/cancer_download/Volume8_No3/395-398%20c_Naieni%204.pdf (accessed December 7, 2012); Peng Xing, Jiguang Li and Feng Jin, "A Case-Control Study of Reproductive Factors Associated with Subtypes of Breast Cancer in Northeast China," *Medical Oncology* 27, no. 3 (2009): 926-931; see also C. Yanhua, A. Geater, J. You, L. Li, Z. Shaogiang, V. Chongsuvivatwong, and H. Sriplung, "Reproductive Variables and Risk of Breast Malignant and Benign Tumours in Yunnan Province, China," *Asian Pacific Journal of Cancer Prevention* 13, no. 5 (2012): 2179-2184; http://www.apocpcontrol.org/paper_file/issue_abs/Volume13_No5/2179-84%204.17%20Che%20Yanhua.pdf (accessed December 7, 2012).

⁴⁹ 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.

⁵⁰ Allen J. Wilcox, Clarice R. Weinberg, John F. O'Connor, Donna D. Baird, John P. Schlatteer, Robert E. Canfield, E. Glenn Armstrong, and Bruce C. Nisula, "Incidence of Early Loss of Pregnancy," *New England Journal of Medicine* 319 (1988): 189-194.

⁵¹ Fern E. French and Jessie M. Bierman, "Probabilities of fetal mortality," *Public Health Reports* 77 (1962): 835-847; Thomas C. Michels and Alvin Y. Tiu, "Second Trimester Pregnancy Loss," *American Family Physician* 76, no. 9 (2007): 1341-1346.

In her first trimester, the mother's ovarian production of estrogen and progesterone (in response to fetal hCG) maintains the pregnancy. If the mother's ovaries do not respond to the hCG, her hormone levels will be insufficient to maintain the pregnancy, and miscarriage will ensue. If the embryo suffers from an abnormality that does not allow sufficient hCG to be manufactured, or if the fetus suffers from an abnormality resulting in its death, miscarriage will ensue. After about 11 weeks' gestation, it is the fetus and placenta—not the mother—that produce most of the needed estrogen and progesterone to sustain the pregnancy.

Often, a mother who spontaneously aborts in the first trimester will remark that she never “felt” pregnant before she miscarried; for example, she may not have experienced any morning sickness or breast tenderness, as she may have in prior pregnancies. The levels of estrogen and progesterone during an abnormal pregnancy that result in a first-trimester miscarriage are insufficient to stimulate breast development. The mother's breasts are therefore unchanged and are not more vulnerable to breast cancer than they were before. In other words, following a first-trimester spontaneous abortion, the mother normally has no change in breast cancer risk,⁵² because her breasts were never stimulated to grow.

Much of the research on reproductive outcomes and breast cancer risk has failed to distinguish between first- and second-trimester miscarriage and has thus caused confusion in the literature—more anon.

Second-trimester miscarriage does increase breast cancer risk.

Second-trimester spontaneous abortions usually occur due to physical problems. For example, the umbilical cord may become twisted around the fetus's neck, leading to fetal death, or the placenta may tear. These second-trimester miscarriages occur among mothers whose estrogen and progesterone levels are normal and whose breasts therefore undergo those changes which increase the risk of breast cancer. Therefore, a mother who experiences a second-trimester miscarriage has an increased risk of breast cancer,⁵³ because her breasts have changed, and because the pregnancy will not continue to term, the natural maturation process that protects the breasts will not be completed.

⁵² 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.

⁵³ Najmeh Tehranian, M. Amelbaraez, R. Salke, and S. Faghizadeh, “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).

Premature delivery before 32 weeks increases breast cancer risk.

Approximately 12.5 percent of all deliveries⁵⁴ are premature,⁵⁵ and approximately 3 percent of all premature deliveries take place before 32 weeks of pregnancy.⁵⁶ If a mother's pregnancy does not continue past 32 weeks due to premature delivery, she will not get the protective effect of pregnancy against breast cancer, because her breast tissue will not have developed enough Type 4 cancer-resistant lobules. *In fact, her risk of breast cancer will be higher than that of a nulliparous (childless) woman, because her pregnancy has stimulated the development of more cancer-vulnerable Type 1 and Type 2 lobules and has thereby created more places for cancers to start (without the mitigating protective processes that are achieved with pregnancy lasting 32 weeks or more).* Several studies have shown that premature delivery before 32 weeks more than doubles breast cancer risk.⁵⁷ Compared to a nulliparous woman or a woman who has experienced pregnancy past 32 weeks' gestation, there are more sites in a woman's breast for cancers to develop following a premature delivery or second-trimester miscarriage before 32 weeks, at which point, sufficient numbers of Type 1 and Type 2 lobules have matured into Type 4 lobules.

E. Induced Abortion and Breast Cancer Risk

Induced abortion increases breast cancer risk.

If a woman has an induced abortion prior to 32 weeks but after 20 weeks, she has the same vulnerability as a woman delivering prematurely before 32 weeks, because her breasts will not have developed enough Type 4 lobules to protect her against breast cancer. If a woman has an induced abortion before 20 weeks' gestation, she will have the same vulnerability as a woman experiencing a non-hormonal spontaneous abortion. Her breasts will have commenced proliferation of Type 1 and Type 2 (cancer-vulnerable) lobules but will not have experienced the protective processes that mitigate this change.

Long gestation before induced abortion increases breast cancer risk.

The longer a woman is pregnant before an induced abortion, the more cancer-vulnerable Type 1 and Type 2 lobules she will develop, and the higher will be her risk for breast cancer.

⁵⁴ Institute of Medicine, Committee on Understanding Premature Birth and Assuring Healthy Outcomes, *Preterm Birth: Causes, Consequences and Prevention*, eds. Richard E. Behrman and Adrienne Stiith Butler (2007), 1; http://books.nap.edu/openbook.php?record_id=11622&page=1 (accessed January 16, 2013).

⁵⁵ A premature delivery is one taking place before 37 weeks' gestation.

⁵⁶ Institute of Medicine, Committee on Understanding Premature Birth and Assuring Healthy Outcomes, *Preterm Birth: Causes, Consequences and Prevention*, eds. Richard E. Behrman and Adrienne Stiith Butler (2007), 75; http://books.nap.edu/openbook.php?record_id=11622&page=75 (accessed January 16, 2013).

⁵⁷ 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; C.C. Hsieh, J. Wu, M. Lambe, D. Trichopoulos, H.O. Adami, and A. Ekblom, "Delivery of Premature Newborns and Maternal Breast Cancer Risk," *The Lancet* 353 (1999): 1239.

Induced abortion increases risk of premature delivery.

When a woman gives birth naturally, it takes many hours to dilate the cervix. During an abortion, the cervix is forcibly dilated and subjected to injury, and this damage to the cervix may cause a woman to later have a premature delivery. Two large meta-analyses show that induced abortion increases a woman's risk of premature delivery.⁵⁸ Furthermore, the more induced abortions a woman has, the higher is her risk of subsequent premature births.⁵⁹

This line of research led the Institutes of Medicine in 2006 to list induced abortion as an "immutable" cause of increased risk of premature birth.⁶⁰ As noted above, this increased likelihood to deliver prematurely may affect a woman's future breast health. For example: The breast cancer risk of a woman whose first pregnancy ends in abortion and whose first birth occurs before 32 weeks' gestation (due to damage from her abortion) may actually be transiently increased, rather than decreased, by her first birth.

F. Full-Term Pregnancy and Breast Cancer Protection

If a pregnancy is healthy and lasts past 32 weeks, even should a mother deliver prematurely, she will have partial protection against breast cancer. Pregnancy lasting 32 weeks is protective against breast cancer, as noted earlier, and between 32 and 40 weeks' gestation, she will gain an additional 11 percent reduction in breast cancer risk.⁶¹ If a mother delivers at 40 weeks, which is "full term," about 70 to 90 percent of her mammary glands will be composed of fully mature Type 4 lobules.⁶² (Though Type 4 lobules are completely mature, not all the breast tissue matures: 10 to 30 percent remain Type 1 and Type 2 lobules and thus remain cancer-susceptible.) This is why a full-term pregnancy is a known and significant protection against breast cancer. Furthermore, as

⁵⁸ P. Shah and J. Zao, on behalf of Knowledge Synthesis Group of Determinants of Preterm/LBW Births, "Induced Termination of Pregnancy and Low Birthweight and Preterm Birth: A Systematic Review and Meta-Analyses," *British Journal of Obstetrics and Gynaecology* 116, no. 11 (2009): 1425-1442; Hanes M. Swingle, Tarah T. Colaizy, M. Bridget Zimmerman, and Frank H. Morriss, "Abortion and Risk of Subsequent Preterm Birth: A Systematic Review and Meta-Analyses," *Journal of Reproductive Medicine* 54 (2009): 95-108.

⁵⁹ 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.

⁶⁰ Institute of Medicine, Committee on Understanding Premature Birth and Assuring Healthy Outcomes, *Preterm Birth: Causes, Consequences and Prevention*, eds. Richard E. Behrman and Adrienne Stith Butler (2007), Appendix B, Table 5, 519; http://books.nap.edu/openbook.php?record_id=11622&page=625 (accessed January 16, 2013).

⁶¹ 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.

⁶² J. Russo, Y.-F. Hu, X. Yang, and I. Russo, Chapter 1: "Developmental, Cellular, and Molecular Basis of Human Breast Cancer," *Journal of the National Cancer Institute Monographs* 27 (2000): 22. See also 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).

stated earlier, each pregnancy after her first reduces a mother's risk of breast cancer by an additional 10 percent.⁶³

Despite the protective effect of a full-term pregnancy, with the maturation of breast tissue from predominantly cancer-vulnerable Type 1 and Type 2 lobules into cancer-resistant Type 3 lobules, it is known that some parous women will still get breast cancer. Type 3 lobules are the predominant lobule in premenopausal parous women; but interestingly, when in one study the breast tissue of parous women who got breast cancer was examined and compared to parous women who did not get breast cancer, Type 1 rather than Type 3 lobules were predominant.⁶⁴ Ductal cancers occur in Type 1 lobules. Also to be noted is that these women either had a late first full-term pregnancy or a family history of breast cancer. The maturation capability of these Type 1-dominant parous women who develop breast cancer may be deficient.⁶⁵ These findings are consistent with other studies that show the importance for cancer resistance of breast development through full-term pregnancy.

As stated earlier, it is only after 32 weeks' gestation that the elevated levels of hPL, in concert with other pregnancy hormones, allow the full maturation of cancer-resistant breast tissue to occur. Therefore, whether a pregnancy ends before 32 weeks with a premature birth, a second-trimester miscarriage,⁶⁶ or an induced abortion, a woman's risk of breast cancer is increased. In all three events, the woman's breasts have been exposed to the same pregnancy hormones (estrogen, progesterone, and hCG). Elevated levels of estrogen and progesterone cause more cancer-vulnerable breast tissue to form, and this tissue's natural maturation process is arrested. By contrast, full-term pregnancy and lactation bring most of the lobules in the breast to full maturity and provide protection against breast cancer.

G. Summary of Breast Cancer Risks and Protections

Given what is known of breast physiology, we can conclude that the following factors are protective, or decrease the likelihood that a woman will develop breast cancer:

- Full-term pregnancy or pregnancy lasting longer than 32 weeks
- Multiparity (more than one full-term pregnancy)
- Short period ("susceptibility window") between menarche and first full-term pregnancy
- Full-term pregnancy soon after abortion or second-trimester miscarriage

⁶³ Mats Lambe, Chung-cheng Hsieh, Hsiao-wei Chan, Anders Ekblom, 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.

⁶⁴ J. Russo, A.L. Romero, and I.H. Russo, "Architectural pattern of the normal and cancerous breast under the influence of parity," *Cancer Epidemiology, Biomarkers and Prevention* 3 (1994): 219.

⁶⁵ R.B. Dickson, J. Russo Chapter 2: "Biochemical Control of Breast Development," in *Diseases of the Breast*, eds. Jay R. Harris, Marc E. Lippman, Monica Morrow, and C. Kent Osborne, 2nd ed. (Philadelphia: Lippincott Williams & Wilkens, 2000).

⁶⁶ During which women generally have normal hormonal levels. See Section II, D for further explanation.

- Breastfeeding

The following factors increase the probability of a woman developing breast cancer:

- Nulliparity (childlessness)
- Long span of time (“susceptibility window”) between menarche and first full-term pregnancy
- Second-trimester miscarriage (spontaneous abortion after 13 weeks of pregnancy)
- Premature delivery before 32 weeks of pregnancy
- Induced abortion
- Induced abortions or second-trimester miscarriages before first full-term pregnancy
- Repeated induced abortions or second-trimester miscarriages

Now we will transition from this review of what we know at the micro-level of biology to examine demographic patterns at the macro-level.

III. Epidemiological and Ecological Epidemiological Studies of the Induced Abortion-Breast Cancer Link

In this segment, 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. Some do not find a link, and many of these are particularly flawed in their design. 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 those who deny the induced abortion-breast cancer link assert is the primary flaw undermining case-control studies. We here try to diligently apply the basic rigorous requirements of statistics and show, sometimes briefly, sometimes at length, how these studies are at variance with standard statistical protocol.

A. Common Biases and Problems in Epidemiological Studies of Induced Abortion and Breast Cancer

Many study design errors can skew the results of epidemiological studies. Below we list some of these biases and problems, note the studies in which they seem to appear, and explain how they might affect studies’ results. We devote attention to the issue of recall or (differential) reporting bias (between cases and controls) in Section III, E.

1. Incomplete questionnaires, low user response, and unsuitable circumstances for obtaining data

Ensuring that the data analyzed in a study were properly obtained is essential, and many studies do not make certain that the information they analyze was appropriately obtained. In one very large study, over half of respondents did not completely answer the study’s question on abortion history. (Some answered the half of the question about spontaneous abortion but not the half about induced abortion, and some answered the

half of the question about induced abortion but not the half about spontaneous abortion.) Rather than leaving these questions half-blank, the authors filled in the blank halves of their responses with “no” (see our analysis of Michels [the Harvard Nurses’ Study]). Another analysis relied on a large national survey to which over 60 percent of those invited to participate declined (see our analysis of Braüner). In both these cases, the massive lack of response should have eliminated the dataset from use.

Many studies relied on interviews conducted in the home (see our analysis of Rohan, referenced in Andrieu; Meirik, referenced in Lindefors Harris; Rookus) or over the telephone (see our analyses of Pike and Khachatryan). While perhaps not every study can be conducted in a clinical setting, data obtained through interviews at home or over the telephone may be affected by some degree of reporting bias. (It is possible that a respondent would be uncomfortable disclosing some personal details in front of a spouse or children in the home or to a stranger over the telephone.) This bias will not necessarily differ between cases and controls, but it may skew the study’s results (likely away from linkage of induced abortion and breast cancer).

2. *Health bias or survivor bias*

The general problem in epidemiological tracking of events that occur at various points over a long time is not, in general, recall bias (that is, differing rates of reporting between cases and controls). Respondents tend to be able to recall important medical events (if imprecisely), and there is no evidence to support the suggestion that cases report induced abortions more consistently than controls.⁶⁷ Rather, there is a massive, systematic bias whenever one, in retrospect, looks only at persons who have survived in health up to a certain time period. That is, one has no information on, and cannot at all hope to even discover, those people who have been selected out of a cohort, or group (at the time of survey), because of their very illness.

Proper statistics is interested in the physical life course of all exposed persons (relative, of course, to the life courses of controls). If the life courses of those who have fallen ill prior to the commencement of the study period are excluded, clearly, a large amount of centrally interesting information on the exposure and disease progression has been dropped. The information of those already sick (and who may have been exposed) is what is dropped, and this information is much of what is of interest.

In the case of abortion and breast cancer, this problem arises from the etiology of breast cancer. Abortions are procured during reproductive years. Average cancer cell doubling times indicate that abortion’s effects would manifest a decade or so after exposure to this risk factor. A woman who procures an abortion and is diagnosed with breast cancer may be excluded from survey consideration at any time after that decade

⁶⁷ See Section III, E, for a full explanation.

or so because she has fallen ill (or died)—of breast cancer.⁶⁸ She, in this case, will not be accounted for, and it is her illness precisely with which we are concerned. Again: 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.*

Angrist and Pischke's *Mostly Harmless Econometrics*⁶⁹ explains of this phenomenon that “[t]he observed difference in health status [...] adds to [this] causal effect a term called selection bias.” When women are selected out of an analysis through their death or are excluded because of previous diagnosis of breast cancer, selection bias may alter the results of the analysis concerned. The authors continue, “...*The selection bias may be so large (in absolute value) that it completely masks a positive treatment effect [e.g., an induced abortion]. The goal of most empirical [economic] research is to overcome selection bias, and therefore to say something about the causal effect of a variable like [a medical procedure]*” [emphasis added]. In order to actually determine whether induced abortion confers any increase to women's breast cancer risk, researchers must aim to eliminate confounding factors, in particular the exclusion of women who have actually been diagnosed with the disease of interest.

It should also be noted that further statistical treatment is necessary to correct the case where women develop breast cancer *prior to* all abortions and are diagnosed with breast cancer after those abortion[s]. Among these women, whether their later diagnosis is another primary [new] breast cancer or a re-emergence of the first breast cancer may not be discernable. These [rare] cases should not be excluded, or “left-censored,” simply because they *also* developed the disease of interest before the exposure of interest, but they do require special statistical treatment from other cases.

The results of this survivor or “health” bias—sometimes called “right-censoring”—are likely to be worse in studies with representative population samples than in case-control studies, in studies whose populations are older, and in studies that deliberately eliminate women with cancer (or specifically, breast cancer) history. Several studies exclude women with a previous history of cancer, in general, or with a previous history of breast cancer, including the Brewster study, the Michels study, the Henderson study (also known as the California Teachers Study), the Braüner study, and the Pike study. In the Ewertz and Duffy study, cases and controls with a previous history of breast cancer,

⁶⁸ Indeed, in the same statistical vein, in their 2012 study, Lecarpentier et al. note that “we cannot exclude that our findings on parity, breast-feeding and incomplete pregnancies are affected by a potential survival bias.” They cannot be certain that some women's information is not lost, because they conducted some interviews long after their subjects had been diagnosed with breast cancer, during which time some may have died and thereby made themselves unavailable for interview. See Julie Lecarpentier, et al., “Variation in breast cancer risk associated with factors related to pregnancies according to truncating mutation location, in the French National BRCA1 and BRCA2 mutations carrier cohort (GENEPSO),” *Breast Cancer Research* 14, issue 4, R99 (2012): 10; <http://breast-cancer-research.com/content/pdf/bcr3218.pdf> (accessed December 21, 2012).

⁶⁹ Joshua D. Angrist and Jorn-Steffen Pischke, *Mostly Harmless Econometrics: An Empiricist's Companion* (Princeton, NJ: Princeton University Press, 2008), 15.

deceased cases, and some cases not notified in time were excluded. The Daling study confined its sample to women experiencing a first diagnosis of *in situ* or invasive breast cancer. The Andrieu multiple re-analysis showed that the Rohan study restricted its analysis to cases with first diagnoses of breast cancer and the Luporsi study excluded women with a history of breast cancer as controls, and malignant controls included in the Clavel study were excluded from the Andrieu multiple re-analysis itself. The Lipworth study, the Becher study, and the Xing study excluded women with previous diagnoses of breast cancer from their control population. The Ozmen study excluded women with “hormonal diseases” from their control group, and the Khachatryan study excluded women with a history of breast diseases or (non-cosmetic) surgeries from their control group.⁷⁰ These survivor or health biases could have skewed the study’s results away from induced abortion-breast cancer linkage.⁷¹

In addition to the problems noted in the above studies, the Laing study, the Fioretti study, the Tehranian abstract, the Naieni study, the Dolle study, and the Jiang study are also designed such that this selection bias may have affected their results.

Similarly, some studies exclude *in situ* breast cancer.⁷² Through the exclusion of *in situ* breast cancer, authors exclude women who have already been affected by the disease of interest. This exclusion may skew the study’s results away from a linkage between

⁷⁰ Women with proliferative breast disease are more likely to have had previous surgery. Proliferative breast disease, although benign, carries an increased risk of breast cancer.

⁷¹ The exceptions are the earliest studies that affirm the induced abortion-breast cancer link that do not assess the relationship in multivariate regressions, such as the 1981 Pike study. If the correlation between induced abortion and breast cancer exists, a univariate bias in these earliest studies (throwing out cancerous women in the control group) throws out aborting women (in the control group). Because the control group has even fewer induced abortions now (in proportion to the levels cases exhibit), the statistic shows an even stronger correlation (more effect) between induced abortion and breast cancer: Throwing out cancerous controls would bias the effect of induced abortion upward. If there is no correlation between induced abortion and breast cancer, throwing out women with cancer would not throw out any extra aborting women (in proportion) in the control group. Abortng women (not being any more likely to have, or to have had, cancer than the other controls) are dropped with the same frequency as the other controls: Throwing out controls with cancer would not bias the analysis.

⁷² *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.

induced abortion and breast cancer. The 2009 Dolle study chose to exclude *in situ* cancer to facilitate a focus on triple-negative breast cancer, but the exclusion of *in situ* cancer is generally not explained in the methodology of the studies from which it is excluded (see our analyses of Melbye [the Danish study], Brewster, Beral, Michels, and Henderson).

Some studies attempt to mitigate the effects of health or survivor bias. As we note above, Pike et al. excluded deceased cases and controls with a history of malignancy, and the Bu abstract and the Dolle study are designed to look backward at women's histories, but they attempt to reduce health or survivor bias by limiting their samples to women who are either still in their reproductive years or who have just completed them. Though the Becher study excluded women with previous diagnoses of breast cancer, it included only cases diagnosed by age 50. The Naieni study also looked backward and examined cancer patients' histories, but they interviewed family members of deceased patients in an attempt to attenuate the problem of women selecting out of their sample.

To avoid corrupting their analysis with health bias or survivor bias, studies should start with the natural course of events. To most clearly show the effects of exposure to induced abortion, they should start with the induced abortion (the exposure) and track the cumulative (relative) risk of falling ill to breast cancer thereafter—perhaps up to two decades. Researchers should not exclude cases or controls who have, or who have had, breast cancer.

3. *Incorrect time frames*

One common methodological flaw in studies of induced abortion and breast cancer relates to the biology of breast cancer. Cancers begin with an individual cancer cell that doubles and reproduces itself over time. It takes an average of eight to 10 years for a breast cancer cell to grow into a clinically detectable cancer one centimeter in diameter.⁷³ Thus, if an abortion in an 18-year-old causes a breast cancer cell to form, it is not likely to be detectable until she is at least 26 years old. However, many studies, in designing their questionnaires and regressions, fail to account for this aspect of breast cancer's pathology.

Some studies issue questionnaires over the span of a decade or so and receive reports of induced abortions over that time (see our analysis of Michels). However, many induced abortions are not followed for sufficient time (at least eight to 10 years) thereafter, and though they may eventually produce detectable breast cancer, they do not do so in the too-brief follow-up time after they are reported. Failure to follow study participants for at least eight to 10 years after an induced abortion (see our analysis of Howe) skews the data away from linkage of induced abortion and breast cancer.

Other studies design regressions (statistical routines that “best compute” how and how much multiple factors simultaneously relate to an outcome) to assess the relationship between time frame after an induced abortion and development of breast cancer. Wrongly-bounded time frames (e.g., “less than one year,” “one to four years,” and “five

⁷³ 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.

or more years” since an induced abortion) could obscure the effect of induced abortion (see our analysis of Melbye). The durations of the first two example categories above ignore the reality that breast cancer resulting from an induced abortion will likely not be detectable in fewer than eight years. The third category would contain abortions not followed long enough (those five to seven years in the past) and those followed long enough (those eight or more years in the past); combining induced abortions followed for adequate and inadequate periods of time into one category could statistically obscure the effect of induced abortion.

An appropriate set of time frames would consider the pathology and development of breast cancer and would isolate the years in which an incidence of breast cancer resulting from an induced abortion would most likely become detectable. For example, a regression that categorized women who had had induced abortions into the following groups would clarify induced abortion's effect on breast cancer risk: zero to seven years after an induced abortion, eight to 15 years after an induced abortion, and 16 to 23 years after an induced abortion.

4. Unsophisticated analysis and unsuitable comparisons

Some analyses assess the influence of having any history of induced abortion on breast cancer risk but perform no more analysis (see our analyses of Melbye, Laing, Khachatryan, Becher, Tehranian, Naieni, Dolle, Xing, Ozmen, and Jiang).

Such assessments are unsophisticated, because as we have stated before, it is not merely the procurement of the abortion that determines the degree of harm it will inflict on a woman's health. The number of abortions a woman procures, a woman's parity status at the time she has an induced abortion, the age at which she procures the abortion, and the gestational stage at which the induced abortion occurs all determine how harmful it will be to her health, in concert with other aspects of her medical history. All these factors must be considered in a truly rigorous study of the effects of induced abortion on breast cancer risk. It is necessary to carefully distinguish between women based on the circumstances of their abortion. Assessing all induced abortions together constitutes combining, into one group, women whose abortions are potentially extremely harmful to their health and women whose abortions are potentially less harmful to their health.

For example, a young teenager who procures an abortion (and does not experience full-term pregnancy until age 30) may do much greater damage to her future breast health than a woman in her twenties procuring an abortion after multiple full-term pregnancies. Analyzing these women in the same cohort is poor research method and tells the reader little. That the danger one woman experiences is statistically “washed out” or weakened by the reduced danger another experiences is not equivalent to finding that induced abortion confers no or little real increase to breast cancer risk. A study that conducts such unsophisticated analyses and fails to fully distinguish women based on the circumstances of their induced abortion will thus fail to fully assess the risk abortion poses to specific sets of women.

Additionally, it is essential that correct reference groups⁷⁴ are established in order to correctly assess the influence of induced abortion on breast cancer risk. For example, the full effect of induced abortion on nulliparous women will not be evident if their breast cancer risk is compared to the breast cancer risk of nulliparous women who have never had abortions (that is, never-pregnant women). This is because, as has been known for centuries, the breast cancer risk of never-pregnant women is greater than that of parous women. The comparison of aborting nulliparous women to only never-pregnant women is unsuitable (see our analyses of Beral, Michels, and Henderson). These women must also be compared to parous women with no abortion history.

The use of an incorrect reference group may also, for example, obscure the magnitude of the effect of repeated induced abortions. The effect of multiple induced abortions may be muted if compared with the effect of one induced abortion. This comparison shows nothing about the risks of repeated induced abortions relative to society's norm (that is, having no induced abortion history). To determine the effect of multiple induced abortions on breast cancer risk, women with repeated induced abortions should be compared to parous women with no induced abortions (see our analysis of Melbye).

5. 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. In attempting to work around differing legal environments, some have made large errors.

One study, whose start and end dates straddled a change in the abortion law, controlled for the time period in which an abortion was procured and thereby controlled for liberal abortion law *and, by proxy*, controlled *out* for abortion. By controlling for freer access to abortion, they controlled out for induced abortion. Furthermore, they did not report the effect that using this control had on their regression's results. In so doing, it is likely that they eliminated the effect of induced abortion on breast cancer from their results (see our analysis of Melbye).

Another study established a comparison between observed and expected number of breast cancers (see our analysis of Goldacre). The "expected" breast cancer incidence comes from the general population's rate and the "observed" incidence comes from aborting women, but induced abortion's general availability and legality during the only reproductive years of the younger women in the cohort combined with the generally

⁷⁴ 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.

lower number of breast cancers diagnosed in young women means that the “observed” category will not have breast cancer rates representative of the actual risk conferred by induced abortion.

Some studies include breast cancer cases diagnosed over a set period of time and assess whether these women previously had induced abortions. Assessing the influence of induced abortion in this rearward-looking manner is problematic, as we have already explained in our subsection on health or survivor bias, but it is more so if the law regulating induced abortion changed markedly during the reproductive years of a study’s participants (i.e., the years a study’s participants would have been having induced abortions, if any). Abortion’s legality may affect how accurately its incidence is reported. Though any inaccuracy in reporting would not necessarily differ across cases and controls, registry data might be incomplete and respondents could be inclined not to disclose illegal abortions in interviews (see our analyses of Pike, Ewertz and Duffy, Howe, Laing, and Daling).

6. Omitted variable bias

Omitted variable bias is the bias that is introduced into epidemiological studies when authors fail to fully specify their model. In other words, by failing to include some risk factor for a disease in their model, another related risk factor may appear to be more important than it actually is. For example, if most women with a history of induced abortion in a given study also had multiple children, an analysis that failed to control for number of live births could show induced abortion to have a too-small effect. Likewise, failing to control for age at first full-term pregnancy could shift undue weight to oral contraceptive use, if measured (because oral contraception is generally used to delay or avoid pregnancy).

The models of the studies vary in their completeness, and none of them is perfect. Nearly all fail to include or to show the influence of some potential breast cancer risk factor(s) in their analyses (e.g., Goldacre, Brewster, Braüner, Ewertz and Duffy, Howe, Laing, Naieni, Dolle, Jiang, and Huang; additionally, Bu and Tehranian make no mention of various breast cancer risk factors⁷⁵).

As much as possible, it is extremely important for studies to control for all potential factors for breast cancer in their analyses. 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.

⁷⁵ Note that only abstracts for the Bu and Tehranian analyses were available.

- **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.** Personal 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.

7. *Incomplete reporting and distinguishing between spontaneous and induced abortions*

In some studies, the data referenced fail to distinguish (see our analysis of Segi), or to distinguish completely (see our analyses of Goldacre and Huang), between women having spontaneous and induced abortions. In some cases, abortions were reported by the woman as spontaneous when medical records note that they were induced (see our analysis of Howe).

Other studies fail to distinguish between induced and spontaneous abortions in their analyses (i.e., the data specify the distinction, but the authors do not in their analysis; see our analysis of Pike). Many studies distinguish between induced and spontaneous abortion when assessing the general effect of abortion history, but when they attempt more sophisticated analysis (such as assessing the effect of abortion relative to the timing of first full-term pregnancy or the gestational period at which it occurs), fail to distinguish between induced and spontaneous abortion and instead assess the two together in one category (see our analyses of Ewertz and Duffy, Andrieu, and Fioretti).

Researchers may do so due to a too-small sample size, but the results of such an analysis are nonetheless of very limited use to the reader.

Note that some studies fail to even include spontaneous abortion as a variable in their analyses (see our analysis of Braüner; Dolle and Becher make no mention of miscarriage in their articles). This is yet another example of authors failing to fully specify their models and include all potential breast cancer risk factors.

8. *Publication bias*

In our review, we found evidence of two forms of publication bias: the unsystematic exclusion of certain datasets from meta-analyses and the baseless dismissal of results that proceeded from re-analysis of case-control studies (see our analysis of Beral). Clearly, statistics demand that the exclusion of data must be done scientifically, and adequate cause must exist for the results of dozens of studies to be dismissed.

9. *Insufficient sample randomization*

If a study's sample is not representative of the general population, then the study's results are not generalizable to the general population. For example, if a study's sample is entirely composed of women of one socioeconomic stratum or of one race, then its results will not be generalizable to women of other socioeconomic strata or races. Thus, randomization—ensuring that a study's sample is representative—is very important. The Pike study and the Daling study include only white women, and the Laing study includes only African-American women. Braüner et al. and Bu et al. confined their studies to parous women, and Fioretti et al. confined their study to nulliparous women. The sample in the Michels study is comprised of mainly white nurses, and the sample in the Henderson study is confined to teachers. These studies' restriction to women of one, or mostly one, racial, professional, educational, or parity class would limit their generalizability.

10. *Very small sample size*

If a study's sample size is small (e.g., Pike, Bu, Tehranian, Khachatryan), it may be difficult to ensure that it is sufficiently randomized, and its applicability to the general population may be limited. Furthermore, assessment of the relationship between induced abortion and breast cancer requires no small amount of analysis and distinguishing of women based on various characteristics, such as those related to parity, oral contraceptive use, and other demographic factors. A too-small sample may result in the inability to distinguish women around these characteristics, because the resulting categories could be too small for any "signal" to be perceptible above fluctuations (in responses) from other sources of error (see our analysis of Ewertz and Duffy).

11. *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 (e.g., Goldacre, Beral, Henderson, Howe, Laing, Lipworth, Andrieu, Fioretti, Naieni, Xing, Ozmen, and Jiang). Though this will have little bearing on the accurate assessment of the relationship between induced abortion and breast cancer, the

distinction between first- and second-trimester spontaneous abortions is an important one. It is imperative that studies make this distinction in their analyses whenever the available data make it possible, because first- and second-trimester spontaneous abortions generally have very different causes. The failure to analyze first- and second-trimester spontaneous abortions separately will degrade the signal of any associated breast cancer risk, so a non-significant finding is more likely to result. As we note in the section on biology, later spontaneous abortions (those not due to hormonal insufficiencies but to physical problems, e.g., the umbilical cord wrapped around the fetus's neck) may increase risk of breast cancer. The breast cancer risk conferred by spontaneous abortions *not* occurring due to hormonal insufficiencies (e.g., those resulting from an umbilical cord twisted around the fetus's neck or from a torn placenta) is indirect evidence of the effect of induced abortion.

12. Incomplete explanation of model

A study may fail to explain how its authors arrived at their conclusions mathematically. For example, one study incompletely explained its model, which involved a comparison of the number of observed breast cancer cases to the number of expected breast cancer cases. The authors failed to explain how they had derived this expected number of cases (see our analysis of Goldacre). In the cases of the Bu analysis and the Tehranian presentation, where only abstracts were available, the mode of the authors' analysis is also unclear.

B. Epidemiological Studies That Do Not Support an Induced Abortion-Breast Cancer Link, With Analyses

Often, those who deny the abortion-breast cancer link will cite the findings of a well-publicized study, such as the Melbye study (the Danish study), the Beral re-analysis, the Michels study (the Harvard Nurses' Study), or the Henderson study (the California Teachers Study), as the basis of their argument. However, careful scrutiny shows these studies were all seriously flawed.

1. 1997 Melbye study (the Danish study)

In January 1997, the Danish Melbye study was published in the prestigious *New England Journal of Medicine*.⁷⁶ This paper is often used in major textbooks to show there is no link between abortion and breast cancer.⁷⁷ The study was hailed by National Cancer

⁷⁶ 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.

⁷⁷ Katherine W. Reeves, Alana G. Hudson, and Victor G. Vogel, "Chapter 19: Epidemiology of Breast Cancer" 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), 333-348.

Institute epidemiologist Patricia Hartge⁷⁸ in an editorial accompanying the study: “In short, a woman need not worry about the risk of breast cancer when facing the difficult decision of whether to terminate a pregnancy.”⁷⁹ She proclaimed that the study had settled the question and that induced abortion did not increase the risk of breast cancer. Despite Hartge’s praise, the Melbye study had several significant flaws.

The Melbye study is insufficient to answer the question of whether induced abortion has any adverse effect on women: It devotes a mere paragraph of text and one unsophisticated comparison to assess the effect of induced abortion (relative to no abortion history), it employs unsuitable comparisons to assess the influence of the number and timing of abortions procured, it possibly eliminates all effect of induced abortion by controlling for the time period at which abortions were procured, excludes women with *in situ* breast cancer, and fails to consider the pathology of breast cancer in assessing the time frame in which the disease would manifest itself following an induced abortion.

- **Unsophisticated analysis of induced abortion.** The Melbye study states that “[o]verall, the risk of breast cancer in women with a history of induced abortion was not different from that in women without such a history” after adding controls. However, this in-text statement references the only analysis of the difference between women with and without abortion history. This is a remarkably unsophisticated comparison, particularly in light of the detailed comparisons that could have been performed with a sample of 1.5 million women. Note that three studies published before the Melbye study (the 1994 Daling study, the 1995 Andrieu study, and the 1995 Lipworth study) assessed the influence of induced abortion based on its timing related to first full-term pregnancy. Such a crude, “kitchen sink” approach offers no insight to individual women regarding the potential risk abortion would pose to their future breast health.

The authors reserve sophisticated modeling for a table in which they examine the *marginal risks* incurred by women based on the circumstances of their procured abortions. All women examined in this analysis have had at least one induced abortion; none of the women considered are without induced abortion history. Hence, this is not an analysis of the effects of induced

⁷⁸ See Hartge’s biography on the NCI website: “Dr. Hartge has conducted epidemiologic research at the National Cancer Institute (NCI) since 1977, investigating the etiology of lymphoma, melanoma, and cancers of the bladder, ovary, breast, pancreas, and brain. She developed and adapted a variety of methods widely used in cancer epidemiology. She has served as the Deputy Director of the Epidemiology and Biostatistics Program since 1996, and in that position, she has provided scientific direction and oversight to a large and productive program of research. She has championed the creation of multi-institution consortia in cancer epidemiology, co-founding the lymphoma consortium InterLymph in 2001 and chairing the NCI Cohort Consortium from 2006 through 2010.” National Institutes of Health, National Cancer Institute, “Patricia Hartge, Sc.D.,” National Cancer Institute; <http://dceg.cancer.gov/about/staff-bios/hartge-patricia> (accessed January 3, 2013).

⁷⁹ Patricia Hartge, “Abortion, Breast Cancer, and Epidemiology,” *New England Journal of Medicine* 336, no. 2 (1997): 127-128.

abortion history relative to having no abortion history, but of the effects of the *circumstances* of an induced abortion relative to other circumstances.

- **Unsuitable analyses.** To address the effects of repeated induced abortions, Melbye et al. use women who have had only one abortion (76.8 percent of aborting women) as a reference group for women with two abortions (17.1 percent) or three or more abortions (6.1 percent).

The authors' neglect of women without abortion history also results in the lack of a suitable reference group for their analysis of the effects of the ordering of live births and abortions. Women who obtain abortions only after their first live birth are used as a reference group for aborting childless women, women who procure abortions only before their first live birth, and women who procure abortions both before and after their first live birth.

The reference groups used in both the analysis of the effect of number of induced abortions and of timing of the induced abortions are unsuitable. Less than 19 percent of their sample had induced abortion history. The appropriate reference category to assess the effect of number and ordering of abortions is parous women with only full-term pregnancies.

- **Reporting difficulty around abortion law change and control for abortion's legality.** Melbye and colleagues also applied a control that diminished the strength of their findings: Their results are controlled for the time period in which the induced abortion was procured. Abortion became legal in Denmark in 1939,⁸⁰ but the law was changed: It was liberalized in October 1973.⁸¹ The number of abortions in Denmark increased markedly after its laws were liberalized.⁸² This information is crucial to consider, because the induced abortions included in the Melbye study took place between 1968 and 1992. Melbye and colleagues assigned a set of indicator variables, or dummy variables, to the time in which the abortion took place and controlled for the time the abortion was procured via that set of indicator variables in the study. In short, they controlled out for liberal abortion law. Controlling for—and not

⁸⁰ Abortion was legal up to 12 weeks in cases of rape, grave risk to the life or health of the mother, or birth defects. See Katarina Blomqvist, "The rocky road to abortion on demand," KVININFO, Danish Centre for Information on Gender, Equality and Diversity, <http://www.kvinfo.dk/side/680/article/58/> (accessed March 4, 2013).

⁸¹ Induced abortion up to 12 weeks' gestation (and after 12 weeks, in many cases) became legal. See "DENMARK. Law No. 350 of 13 June 1973 on the interruption of pregnancy. (*Lovtidende for Kongeriget Danmark*, Part A, 6 July 1973, No. 32, pp. 993-995)," Berkman Center for Internet and Society at Harvard University; <http://cyber.law.harvard.edu/population/abortion/Denmark.abo.htm> (accessed March 4, 2013).

⁸² In 1968-1972, abortions numbered 6,450 (1968), 7,300 (1969), 9,375 (1970), 11,522 (1971), and 13,667 (1972). In 1973, 16,536 abortions were performed, and in 1974, in the first full year of the law's liberalization, abortions numbered 24,868. Thereafter, the number of abortions fluctuates, but generally stays in the low twenty-thousands. See Wm. Robert Johnston, "Historical abortion statistics, Denmark," Abortion statistics and other data--Johnston's Archive, March 11, 2012, <http://www.johnstonsarchive.net/policy/abortion/ab-denmark.html> (accessed March 4, 2013).

reporting—the influence of the time the induced abortion was obtained masks, and likely eliminates, the effect of induced abortion on breast cancer entirely in their regressions. This design error will statistically dominate all other factors involved in the production of cancer through induced abortion (as their null-response Table 1 shows almost perfectly). This control for the time in which the abortion took place—a control for liberal abortion law, or free(r) access to induced abortion—may have absorbed *all the effect* of induced abortion on breast cancer risk. This may be why, in a study of 1.5 million Danish women, just one explanatory variable—abortion at or past 18 weeks—carries any significance (Table 1).⁸³ This is a serious error in model interpretation. By ignoring the significance of liberal abortion laws when attempting to compare breast cancer risk within a cohort, they failed to realize what Beral and colleagues grasped when designing their own study: So as “to minimize possible differential reporting of illegal abortion, analyses would be restricted, as far as possible, to populations with access to legal abortion services.”⁸⁴

- **Late induced abortion.** As noted above, Melbye’s Table 1⁸⁵ addresses the *marginal* risks incurred based on the circumstances of women who obtain abortions. This table finds no effect based on any of the circumstances examined, with the exception of abortion at or after 18 weeks of pregnancy. Melbye’s analysis shows doubled odds of breast cancer with abortions at 18 weeks’ gestation or later. Again, the additional risk this poses is the *only* significant explanatory variable for induced abortion’s circumstances in the study. Perplexingly, Melbye and colleagues attempt to diminish the importance of this, their *only* significant finding, noting “[t]he fact that such an increase [in risk with second-trimester abortions] did not affect the overall results clearly indicates that it is based on small numbers and therefore requires cautious interpretation.” To have dismissed their only significant finding, rather than

⁸³ Melbye et al. rather misleadingly note that “neither the calendar period at the time of diagnosis of breast cancer (P=0.17) nor the calendar period at the time of induced abortion (P=0.83) modified the relation between induced abortion and the risk of breast cancer.” (See 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): 83.) However, what they show here is merely that the *year in which one procures an induced abortion* has no effect on *individual risk of developing breast cancer*. Their result is unsurprising. The (lower-order) result that they fail to report is *whether the legalization of abortion affected breast cancer incidence*.

⁸⁴ See 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): 1008. Though Beral and colleagues list 1938 as the year in which “legal abortion services” became available in Denmark, as we note earlier, abortion before 12 weeks’ gestation was available only under certain circumstances from 1939-1973.

⁸⁵ 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): 83.

devoting further energy to its investigation, was to disregard the demands of proper statistics.⁸⁶

- **Health or survivor bias.** Melbye et al. risk introducing health bias or survivor bias into their study by excluding women with *in situ* breast cancer; their study was restricted to women with invasive breast cancer.
- **Incorrect time frames.** Finally, the time frames established in the Melbye study for analysis of cancer development in aborting women are not tailored to the specific pathology of cancer growth. The authors analyzed the risk of cancer among women for whom under one year had passed since an induced abortion and for whom one to four years had passed. The cohort for whom five or more years had passed since an induced abortion was established as the reference category. As we note earlier, breast cancer resulting from an induced abortion would not be detectable until approximately eight to 10 years thereafter. Hence, induced abortion was not found to increase breast cancer risk under one or one to four years thereafter. Furthermore, including women in the reference category whose induced abortions were *fewer* than eight to 10 years prior and women whose induced abortions were *more* than 10 to 14 years prior⁸⁷ may have statistically “washed out” any effect. A better classification scheme might, for example, have grouped women who had had abortions seven or fewer years earlier, eight to 14 years earlier, 15 to 21 years earlier, or 22 or more years earlier. Such groupings would be appropriately tailored to the time that breast cancer takes to grow to a detectable size: eight to 10 years.

2. 2001 Goldacre study

The UK Goldacre study⁸⁸ is marked by incomplete reporting and distinguishing of spontaneous and induced abortions; omitted variable bias through the lack of empirical consideration of data on parity, age, and other breast cancer risk factors (and hence no parsing of the effects of differently-ordered abortions); an incompletely specified model; and insufficiently randomized data. Given these flaws, this study is not a significant contribution to the literature.

- **Incomplete reporting and distinguishing of induced and spontaneous abortions.** Furthermore, as the authors note, the records they reference frequently failed to specify whether an abortion was induced or spontaneous. In response to this ambiguity, they developed a category for “all” abortions that lumped together induced and spontaneous abortions with the unspecified abortions. They analyzed the category for “all” abortions alongside the individual cat-

⁸⁶ As John Boyd, famed aerospace engineer and military strategist, used to say, “The most important data are the data that do not fit. That’s where science advances” (paraphrased, from personal conversation with Boyd).

⁸⁷ See Appendix D for further explanation.

⁸⁸ 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.

egories for induced and spontaneous abortions. The authors do not state in what fraction of cases there was uncertainty about the nature of the abortion. This lack of specification could potentially lead to serious exclusion bias in the eventual fit of the model on the data that are kept. Exclusion bias would be created if there were a large number of unspecified abortions and if the reason their type was not specified was correlated with abortion type (which would likely explain any differential rate of cancer development). Any risks associated with spontaneous and induced abortion in this population cannot be clarified unless (as is the standard of comprehensive research work) the statistical answers to *both* of these questions are openly presented. If data (e.g., on parity, gestation, etc.: see below for a further elaboration on these matters) are not available, the onus is on both the researcher and research community to discount the (lack of) finding in any such study.

- **Incomplete model (lack of parity data).** The authors have only incomplete data on abortions and also note that analysis of certain “lifestyle or reproductive variables [was] outside the scope of [their] study.” Among these variables is pregnancy. Though the authors assert that they closely matched control groups to cases for data on “these factors” (e.g., “reproductive and lifestyle variables”), they fail to actually demonstrate that the control groups are closely matched. The demographics of their sample are not detailed in tables or text. The authors do not demonstrate similarity between cases and controls regarding the variables of concern or show any differences between the groups in these regards to be insignificant. This produces an obvious problem: Their model does not account for all risks for developing breast cancer. The exclusion of data on other breast cancer risk factors may add bias (an omitted variable bias) to any attempt to distinguish classes of women at risk.
- **Unsophisticated analysis of induced abortion.** Furthermore, without including data on parity status or pregnancy, it is impossible to parse out the timing and ordering of their cohort’s reproductive events and thereby distinguish the risks for breast cancer that abortion poses for various cohorts of women. A study that fails to differentiate between the effects of differently timed and ordered abortions is less effective than one that does so differentiate. The authors of the Goldacre study do not note (or perhaps their records do not specify) at what stage of gestation the spontaneous or induced abortions took place.
- **Reporting difficulty around abortion law change, sample age, and expected number of abortions.** The women with tabulated breast cancer incidence under investigation include some cohorts without many abortions during their fertile years (older women, who were fertile before abortion was legal in the UK) and those with relatively many during their fertile years (younger women, fertile after abortion was legal). Even though age is strati-

fied (analogous to controlling for age), the re-combination of these cohorts' incidence rates will interact age (one being older or younger) with abortion.⁸⁹

Goldacre's "expected" breast cancer incidence comes from the general population's rate (though they do not explain how this number is derived). Their "observed" breast cancer rate is what they measure for those who have had an abortion. But the two quoted rates for the general population and aborting women have very different women in them: These statistics aggregate (recombine) women of very different age types. Those having had an abortion are much younger (because abortion was generally available and legal only after 1967). The aborting women, being younger, will exhibit (what is "observed" in their class) lower breast cancer rates. Younger women get breast cancer much less frequently than older women.

Once (what appears to be) the window has passed for a breast cancer to manifest itself (once 14 years or so have passed), these women (older women) show *decreased* risk of breast cancer. The model shows this, albeit imprecisely.

- **Incomplete and insufficiently randomized data.** Finally, the sample suffers from selection bias, as it was confined to women who obtained abortions in hospitals. As Joel Brind notes in a separate review, a mere 300 of the 28,616 cases included in Goldacre (women diagnosed with breast cancer between 1968 and 1998) were classified as having a history of induced abortion—amounting to barely 1 percent of cases over a 30-year period. However, the abortion rate in the UK was over 1 percent per year over that period;⁹⁰ Goldacre et al. may have too few women classified as having induced abortion history. Labeling women who have had an induced abortion as women *not* having had an induced abortion will decrease any measured influence of abortion on breast cancer. The authors admit in their paper that their "data on abortions are substantially incomplete because they only include women admitted to hospital [sic], only include those in the care of the National Health Service,

⁸⁹ Here is a putative interaction. Women in their 30s in the 1960s are only in their 60s in the 1990s. All those older (later 60s, or in their 70s or even 80s) will have statistically unmeasurable abortion rates. (In the 1960s, when abortion was legalized, these older women were too late, relative their fertile period, to demand abortions. The diminished number of abortions in their population is evident: As we note below, whereas barely 1 percent of their cases had an abortion over 30 years, the abortion rate in the UK was over one percent per year across those 30 years!) These older women have a plurality of the breast cancer cases. Older women get more breast cancer. In the calculation of "observed" rates of cancer they will not be counted, because they are unmeasurable. Upon re-aggregating the age stratification, the "observed" category (those with abortions) will lack this contributing population (older women) and so not have representative breast cancer rates, as represented in the Goldacre findings.

⁹⁰ National Cancer Institute. U.S. National Institutes of Health. Summary Report: Early Reproductive Events and Breast Cancer Workshop, Mar 25, 2003; www.cancer.gov/cancerinfo/ereworkshop-report (accessed Oct 17, 2005), as cited in Joel Brind, "Induced Abortion as an Independent Risk Factor for Breast Cancer: A Critical Review of Recent Prospective Studies Based on Prospective Data," *Journal of American Physicians and Surgeons* 10, no. 4 (Winter 2005): 107.

and only in the time and area covered by the study.”⁹¹ Hence, their study is insufficiently randomized.

3. 2004 Beral re-analysis

Valerie Beral’s large “re-analysis” of data from 53 epidemiological studies, including 83,000 women with breast cancer from 16 countries, was published in the British journal *The Lancet* in 2004.⁹² Beral et al. find, in one analysis, that induced abortion *increases* breast cancer risk and that induced abortion *decreases* breast cancer risk in another analysis. The study was hailed by its researchers as the definitive analysis that put to rest the claim that abortion increases breast cancer risk. Beral stated, “Scientifically, this is really a full analysis of the current data.”⁹³ However, a review of the study reveals that it is not a “full analysis” and that serious methodological flaws render the study unreliable.

The Beral re-analysis is flawed by two instances of publication bias: The authors unsystematically dismissed the result of their analysis of retrospective data in favor of their analysis of prospective data, and they unsystematically excluded certain peer-reviewed studies from their analysis. Beral and colleagues also chose an unsuitable reference group to assess any influence of induced abortion on breast cancer, excluded studies including women with *in situ* breast cancer, and failed to distinguish between first- and second-trimester spontaneous abortions.

- **Induced abortion.** Beral and colleagues found induced abortion history contributed to a statistically significant *decrease* in breast cancer risk in their meta-regression of studies based on prospectively collected data and a statistically significant *increase* in breast cancer risk in their meta-regression of studies based on retrospectively collected data.

No significant influence was found, in prospectively collected or in retrospectively collected data, for two or more induced abortions relative to one induced abortion, for experiencing a first induced abortion before age 25 relative to after age 25, for an induced abortion being fewer than 10 years in the past versus an induced abortion being 10 or more years in the past, or induced abortion before versus after giving birth.

- **Spontaneous abortion.** The Beral re-analysis found no significant effect for spontaneous abortion in either their analysis of studies based on prospective data or in their analysis of studies based on retrospective data.
- **Publication bias.** As we explain above, the Beral study is marked by several flaws, including two types of publication bias. The first type is the dismissal of

⁹¹ 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): 337.

⁹² 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.

⁹³ David Wahlberg, “Study: Breast Cancer Not Tied to Abortion; Group Backs Up Institute’s Earlier Findings,” *Atlanta Journal-Constitution*, March 26, 2004, A9.

findings sourced in retrospective data; the second is the unsystematic exclusion of certain datasets from their meta-analysis.

- **Publication bias: Dismissal of analysis of retrospective data.** Beral and her colleagues divided the studies they analyzed into two separate categories: Those that used retrospective methods of data collection (i.e., information from patients after they were diagnosed with breast cancer and control subjects) and those that used prospective methods (i.e., medical records taken before a breast cancer diagnosis). As noted above, the 39 retrospective studies showed evidence of an *increase* in breast cancer risk with abortion. The 13 prospective studies showed a *decreased* breast cancer risk with abortion. The study concluded from its prospective data that there was no association between induced abortion and breast cancer, and this conclusion was widely reported in the press. Instead of reporting the results of their study accurately, the authors in their conclusion termed the increase in breast cancer risk based on retrospective data “misleading” and asserted that “recall bias” altered the data.⁹⁴ Despite the theoretical possibility that recall bias exists, the studies most frequently referenced as evidence of recall bias are far from sufficient as a basis for this charge, as we will demonstrate in Section III, E.

The authors’ unsystematic dismissal of their findings based on retrospective data is scientifically unjustifiable, because it is arbitrary. Though it is possible that healthy women in retrospective studies underreport their abortions, it is also possible (and the authors admit as much) that underreporting of abortions took place in the prospective studies. They offer no substantiation for their statement that underreporting would not significantly distort prospective studies. Yet the authors do not dismiss the result of their analysis based on prospective data. Rather than dismissing the result of their analysis of retrospective data, they could have built controls for the circumstances under which the data in each study were obtained into their model and thereby controlled for recall bias. They did not. Their dismissal of findings sourced in retrospective data is based on an arbitrarily applied assumption.

The authors state, “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 about the studies that had recorded information on induced abortion retrospectively and prospectively, the collective results 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.” Thus, they simply suppose that recall bias has tainted

⁹⁴ 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.

retrospective studies. They throw out the overall finding of 39 studies because it contradicts the overall finding of 13 studies.

- **Publication bias: Unscientific exclusion of studies.** Beral and colleagues were also unsystematic in choosing which datasets to include and exclude. Beral et al. deliberately excluded a total of 13 peer-reviewed studies from their analysis. They also failed to note the existence at least five published datasets.⁹⁵

The authors included some unpublished studies and some unpublished abortion data in their analysis: “Only about two-thirds of the eligible studies that had obtained relevant information had published their findings on abortion and breast cancer.” Beral and her colleagues take the perspective that by including unpublished data they have avoided the risks associated with (a particular type of) publication bias⁹⁶ (of course, their study is affected by other forms of publication bias). However, because these data were unpublished, readers of the Beral re-analysis can have only limited confidence in its results. The veracity of the datasets has not been established: there is no way of knowing what means were used to arrive at the conclusions reported. It would have been wise to include indicator (dummy) variables to control for any potential differences in published and unpublished datasets.

For example, among the unpublished datasets Beral referenced is a Scottish study showing a decrease in breast cancer risk with abortion. As the study’s data were unpublished, it had not been assessed independently. However, these data were published the following year as the 2005 Brewster study (with Beral as a co-author), which we critique below. That one of the datasets which we can trace is so flawed casts doubt on the others which we cannot review.

⁹⁵ A.E. Laing, G.E. Bonney, L. Adams-Campbell, et al., “Reproductive and Lifestyle Risk Factors for Breast Cancer in African-American Women,” *Genetic Epidemiology* 11 (1994): A300; D.G. Zaridze data (unpublished) in N. Andrieu, S.W. Duffy, T.E. Rohan, M.G. Lê, E. Luporsi, M. Gerber, R. Renaud, D.G. Zaridze, Y. Lifanova, and N.E. Day, “Familial Risk, Abortion and Their Interactive Effect on the Risk of Breast Cancer—A Combined Analysis of Six Case-Control Studies,” *British Journal of Cancer* 72, no. 3 (1995): 744-751; E. Luporsi, “Breast cancer and alcohol,” (PhD thesis, University of Paris-Sud, 1988), data in N. Andrieu, S.W. Duffy, T.E. Rohan, M.G. Lê, E. Luporsi, M. Gerber, R. Renaud, D.G. Zaridze, Y. Lifanova, and N.E. Day, “Familial Risk, Abortion and Their Interactive Effect on the Risk of Breast Cancer—A Combined Analysis of Six Case-Control Studies,” *British Journal of Cancer* 72, no. 3 (1995): 744-751; L. Bu, L.F. Voigt, Z. Yu, K.E. Malone, and J.R. Daling, “Risk of breast cancer associated with induced abortion in a population at low risk of breast cancer,” *American Journal of Epidemiology* 141 (1995): S85 (abstract 337); Lynn Rosenberg, Julie R. Palmer, David W. Kaufman, Brian L. Strom, David Schottenfeld, and Samuel Shapiro, “Breast Cancer in Relation to the Occurrence and Time of Induced and Spontaneous Abortion,” *American Journal of Epidemiology* 127, no. 5 (1988): 981-989.

⁹⁶ The type of publication bias they hope to avoid is the bias in journals against publishing studies with null results (i.e., those that show no effect for a given variable). This bias is a problem in epidemiology, though it does not seem to affect the field of induced abortion research. When a study finds no effect, it is widely discussed and its findings are promoted vigorously; when a study finds induced abortion to have an effect, its findings are often dismissed as the mere result of recall bias.

- **Health or survivor bias.** Notably, the authors included only studies of women with invasive breast cancer and excluded *in situ* breast cancer, the significance of which we address above.
- **Unsuitable comparison.** Another major flaw in the Beral study lay in its choice of reference group. The authors compare the risk of a pregnancy ending in induced abortion with the risk of “never having had that pregnancy.” Their language is unclear, but if Beral et al. here refer to nulliparity, then the breast cancer risk contributed by induced abortion would be muted by comparison to the breast cancer risk posed by nulliparity. Regardless, Beral and colleagues have chosen to assess the wrong counterfactual.⁹⁷ Pregnant women who undergo induced abortion ought not to be compared to hypothetical women not experiencing that pregnancy. They ought to be compared to pregnant women who do not undergo induced abortion but continue their pregnancy to term (controlling, of course, for the effect of parity itself). The comparison the authors employ in their analysis of induced abortion is of no benefit to actual pregnant women, for whom “never having had that pregnancy” is not an option. For the sake of actual women’s breast health, the relevant comparison to a cohort with abortion history is a cohort experiencing only full-term pregnancy.

Note also that inappropriate comparisons were set up for Beral et al.’s more sophisticated analyses. For these analyses, when testing the influence of number of induced abortions, age at first induced abortion, number of years since an induced abortion, or the ordering of induced abortions and live births, the preferred reference group is parous women with no induced abortion history.

- **No distinction between first- and second-trimester spontaneous abortions.** Finally, Beral et al. fail to distinguish, in their analysis of spontaneous abortions, between first- and second-trimester spontaneous abortions.

Given these serious methodological flaws and the confusion this study has caused, the best that can be done is to disregard this piece of research. It did not contribute to the steady march of scholarship or to clarity in epidemiological patterns of breast cancer development. Additionally, the study did much to confuse the uninformed, because Beral is a leading breast cancer researcher in a different genotoxin field, the use of estrogen/progesterone (so-called “hormone treatment” or “hormone replacement therapy”)

⁹⁷ Beral and colleagues attempt to determine what would have happened had these women not experienced the pregnancy that they aborted. This is a counterfactual. “For a given population, a counterfactual asks, ‘What if an identified policy [change] had not happened?’” See Marriage and Religion Research Institute, “Causal Determination for Social Policy: Counterfactuals, Natural Experiments, Population Shifts,” by Henry Potrykus (February 7, 2013); <http://marri.us/causality> (accessed July 18, 2013).

during or after menopause. For her Million Women Study, she was made Dame of the British Empire.⁹⁸

4. 2005 Brewster study

One prospective study used in the much-quoted Beral re-analysis study is the Brewster Scottish prospective study (of which Beral herself was a co-author).⁹⁹ The Brewster study is negatively affected by a glaring lack of data on parity, which diminishes its ability to distinguish the effect of differently timed induced abortions. The Brewster study introduced health bias into its analyses by including only “new incident breast cancers” and excluding women with a previous history of cancer, as well as excluding controls with cancer and women with a history of *in situ* breast cancer.

- **Lack of data on parity.** This study included women “with *all* reproductive events occurring from 1981 onwards[, and] . . . with some reproductive events occurring before 1981, and number of pregnancies equalled number of births—that is, *no miscarriages or induced abortions before 1981* [italics added].”¹⁰⁰ This resulted in an unknown age at first birth for nearly two thirds of cases and controls, though the authors still chose to control for age at delivery of first child in their regressions. The absence of this important information forced the authors to construct the category “unknown sequence” for the purposes of analyzing order of their sample’s reproductive events. Combining women whose parity status at the time of their abortion is unknown is of no benefit in identifying the breast cancer risk that abortion poses to different women.
- **Unsuitable comparisons.** Furthermore, the analysis of the ordering and timing of women’s reproductive events compares nulliparous aborting women, parous aborting women, and women the sequence of whose abortions and pregnancies are unclear to a reference category of women with “no abortion,” without specifying whether these women are parous or nulliparous. Combining non-aborting nulliparous women (who generally have increased breast cancer risk) and non-aborting parous women (who gen-

⁹⁸ The Million Women Study applied the *opposite* methodology from Beral’s abortion reanalysis. Beral and colleagues did not compare women undergoing “hormone replacement therapy” to women their age who were *not menopausal*; they compared them to other women their age who were *menopausal and not undergoing “hormone replacement therapy”*! They employ the latter comparison and not the former because older women who are not menopausal are a higher-risk group, and the increased risk associated with “hormone replacement therapy” would be muted by comparison. However, the former type of comparison (i.e., the comparison between nulliparous women and women with abortion history) is commonly employed among those who study the link between abortion and breast cancer. Joel Brind deals extensively with this matter in his 2007 published testimony to the British Parliamentary committee studying the impact of abortion. See Joel Brind, “Scientific developments relating to the effect of abortion on risk of future breast cancer,” in *Memorandum 14: Scientific Developments Relating to the Abortion Act 1967*, Twelfth Report of Session 2006-7 (London: The Stationery Office Limited, 2007), Ev 96-97.

⁹⁹ 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.

¹⁰⁰ *Id.* at 284.

erally have low breast cancer risk) would produce a non-aborting cohort with a breast cancer risk elevated over that of the ideal reference group. This elevated risk would mute the risk associated with abortion, by comparison.

This comparison employs almost 10,000 women with no induced abortion history, over 1,700 women with an *unclear sequence* of induced abortions and pregnancies, 876 parous (induced) aborting women, and only 155 nulliparous (induced) aborting women. The sequence of approximately two thirds of the (induced) aborting women's reproductive histories is unknown. Almost all aborting women whose reproductive sequence is known (nearly one third—876 of 2,748) experienced the protection of live birth first. Those with unknown sequence are statistically like those who experienced live birth first: Both categories are statistically protective. The remainder, those who procured abortions while nulliparous, is very small (155 of 2,748). If the sequence of abortions and births matters more than parity—parity is used as a control variable in the rest of the table—or age at abortion, then all statistics in the other regressions are determined numerically by this dominating effect and by the omitted variable bias of unknown sequence behaving like live birth first. This will decide all other regressions, because the category composed of women aborting while nulliparous (for the purposes of our paper, the women at risk) gets tiny weight in the regression: 155 women out of 2,748 is one tenth of the size of the group of women the sequence of whose abortions and births is unknown (1,717 of 2,748). The class adding noise (i.e., unknown sequences of abortion and pregnancy) is 10 times larger than the class whose sensitivity to breast cancer we suspect is most acute (because of their being both nulliparous and aborting).

Additionally, two thirds of aborting women are shown to have breast cancer risk reduction resembling those who experience live birth first; but that their fertility information is not coded in any way immediately discernible in the other regressions makes it a huge, lurking factor that can bias all statistics. This may be why Brewster sees protective effects associated with abortion. For example: Procuring an abortion at age 30 or later is found to be significantly protective; but the study participants age 30 or older are likely to be the same participants the sequence of whose live births and abortions are unknown (due to the possibility of live births occurring before 1981).

- **Health or survivor bias.** Finally, Brewster et al. excluded women with any history of cancer or of *in situ* breast cancer prior to their “diagnosis of breast cancer/hospital admission.” The exclusion of women with a previous history of cancer is a health bias that could have introduced a large error into their analyses. No reason is given for the exclusion of *in situ* cancer. Furthermore, controls with cancer were excluded, another bias in their study.

5. 2007 Michels study (the Harvard Nurses' Study)

The Michels study concluded that there was no increased risk of breast cancer with induced abortion.¹⁰¹ Because of the prestigious name of the dataset (the Nurses' Health Study II) and the Harvard University affiliations of some of the authors, the study's conclusions have had massive impact on the induced abortion-breast cancer debate despite its flaws, which are such that the study's conclusion could actually be reversed.

The Michels study suffers from the introduction of massive error through answers supplied by the authors to questions left half-blank, from unsuitable comparisons and the lack of distinction between first- and second-trimester spontaneous abortions, from follow-up time after (some fraction of) induced abortions insufficient to detect cancer, from sampling bias due to the study's focus on educated women, and from health bias or survivor bias from the exclusion of women with a history of previous cancer or of *in situ* breast cancer. These (and possibly other) flaws are serious enough for this study to be, unhappily, discounted.

The Michels study, which is based on data from the longitudinal Nurses' Health Study II, includes over 100,000 female nurses. These women were initially surveyed in 1989. Ninety-two percent of these were white.

- **Induced abortion.** The Michels study found no significant influence for induced abortion on breast cancer risk, whether assessed generally, by number of induced abortions, by age at first induced abortion, or temporally (that is, with respect to the timing of first birth). No effect was distinguished when women were divided by parity status and then re-assessed according to their general induced abortion history and number of induced abortions.

When induced abortions were broken down (among nulliparous and parous women) by potential relationship with specific types of breast cancer, induced abortion among parous women was found to have a positive, significant influence on the risk of PR- (progesterone receptor negative) breast cancer.

- **Spontaneous abortion.** The Michels study found no significant influence on breast cancer risk for spontaneous abortion or number of spontaneous abortions. It did, however, find a significantly protective effect for spontaneous abortions taking place at or before age 19 (but no other age).

No effect for spontaneous abortions was found when women were distinguished by parity status and their general spontaneous abortion history and number of spontaneous abortions were assessed. However, when assessed temporally, spontaneous abortions after first birth were found to have a marginally significantly protective (i.e., negative) influence on breast cancer risk. Spontaneous abortions before first birth were not found to have any significant influence on breast cancer risk.

¹⁰¹ 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.

No effect was detected for spontaneous abortions when they were broken down (among parous women) by potential relationship with specific types of breast cancer.

- **Unsuitable data handling.** However, like many studies showing no effect for induced abortion on breast cancer risk, the Michels study contains many flaws. The statistical analysis section shows that the overall sample size includes more than 100,000 women. However, over 50,000 women neglected to complete the most important question on the baseline questionnaire, that on induced and spontaneous abortion. (Some only answered the half of the question addressing induced abortion, and some only answered the half addressing spontaneous abortion.) Interestingly, the authors note that “[w]e assumed that the women who answered only half of the question did not answer the other question because of an oversight or because they felt that the question did not apply to them.” This assumption—that nondisclosure is evidence of an actual non-history of abortion—is mutually exclusive of the assumption that women intentionally withhold information about their induced abortion histories unless they feel it is necessary (for example, because of breast cancer) to disclose it. Furthermore, it is far from clear that the terse sensitivity analysis performed¹⁰² could correct for such a massive introduction of error as the one caused by nearly half the overall sample failing to answer the central questions in the survey.

Table 2 shows that the class of women with two or more induced abortions is fewer than 40 women. Said differently, there is a ratio of 50,000 total women to 40 women in the category of greatest concern (the women with two or more abortions) in a class of women where there is massive error in response. For this reason, even properly done statistical modeling would hardly be able to conclude anything relevant regarding the effect of repeated abortion on breast cancer risk. This cohort of women is 1,000 times smaller than the group of women through which error has been introduced. The lack of demonstrated effect of repeated induced abortion on breast cancer in this analysis is not a demonstration of non-linkage between the two.

- **Unsuitable comparisons.** Additionally, rather than comparing parous and nulliparous women procuring some number of induced abortions to the key reference group—parous women with only full-term pregnancies—the authors divided their analyses of abortion by parity status and compared nulliparous women who procured induced abortions to nulliparous women who did not procure induced abortions, and parous women who procured induced abortions to parous women who did not procure induced abortions. (Though they elsewhere assess the effect of induced abortion history while controlling

¹⁰² 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): 816.

for parity, this analysis fails to assess whether or not these women had the protection of full-term pregnancy *at the time of their abortion.*)

- **No distinction between first- and second-trimester spontaneous abortions.** Notably, the measures, and thus the analysis, do not distinguish between first- and second-trimester spontaneous abortions.
- **Insufficient follow-up time.** Significantly, subjects who had abortions more than two years after the initial survey, during the study's follow-up time, were classified as having an abortion but were not followed long enough for any resultant cancers to develop to a detectable size. (Eight to 10 years is required for detectable breast cancer to develop after an abortion, based on cell doubling times, and so eight to 10 years is the minimum time required for follow-up.) This increased the number of women in the "abortion class" while decreasing the number of women in the "breast cancer class," a biasing of the outcomes against any abortion-breast cancer link. The authors' proportional hazard models attempt a correction for women followed for a shorter time; however, they do not contain within their formalism the reality posed by cell doubling times—that two or four years is simply not a long enough period to develop detectable breast cancer from an abortion.
- **Sampling bias (non-randomized sample).** Furthermore, the study is marked by sampling bias. The study is 92 percent white and is entirely comprised of female registered nurses, whose IQ (i.e., that of women with at least a Bachelor's degree) is most likely at least one standard deviation higher than that of the general population. No controls are applied for race or for education. In his 2008 essay in *Nature*, University of Edinburgh professor of differential psychology Ian Deary noted that "[i]ntelligence can predict mortality more strongly than body mass index, total cholesterol, blood pressure or blood glucose, and at a similar level to smoking."¹⁰³ Among other things, Deary noted that reduced mortality in high-IQ individuals could be attributed to healthier behaviors. The population studied in the Michels study is not representative of the general population. Hence, though Naieni et al.¹⁰⁴ (and others) have found university education to be correlated with increased breast cancer risk, even results derived from a sound methodology regarding this sample of women would not be generalizable to the population at large.
- **Health or survivor bias.** Finally, women with a previous history of cancer or with a history of *in situ* breast cancers were excluded from the study. No

¹⁰³ G.D. Batty, M.J. Shipley, C.R. Gale, L.H. Mortensen, and I.J. Deary, "Does IQ predict total and cardiovascular disease mortality as strongly as other risk factors? Comparison of effect estimates using the Vietnam Experience Study," *Heart* 94, no. 12 (2008) 1541-1544, as cited in Ian Deary, "Why do intelligent people live longer?" *Nature* 456 (November 2008): 175-176.

¹⁰⁴ Kouros Holakouie Naieni, Ali Ardalani, Mahmood Mahmoodi, Abbas Motevalian, Yoosef Yahyapoor, and Bahareh Yazdizadeh, "Risk Factors of Breast Cancer in North of Iran: A Case-Control in Mazandaran Province," *Asian Pacific Journal of Cancer Prevention* 8 (2007): 395-398; http://www.apocp.org/cancer_download/Volume8_No3/395-398%20c_Naieni%204.pdf (accessed December 7, 2012).

explanation was given for the exclusion of *in situ* breast cancer. Though it is highly unlikely that all 4,065 previously-diagnosed and excluded cancers were cancers of the breast, it is likely that some were. Furthermore, only 1,458 invasive breast cancers were found in the study. Thus it is possible that a large fraction of the total number of breast cancers with which respondents were (at any time) diagnosed was excluded, a health bias that could have skewed their data away from non-linkage of induced abortion and breast cancer.

6. 2008 Henderson study (the California Teachers Study)

The Henderson study¹⁰⁵—another study based on a large, “gold standard” dataset (the California Teachers Study)—concluded that there was no increased risk of breast cancer with abortion. The Henderson study has many weaknesses, including unsuitable comparisons that mute the effect of induced abortion, the survivor or health bias produced by the exclusion of women with previous history of breast cancer and women with *in situ* breast cancer, sampling bias through the confinement of the study to educated women, and failure to distinguish between first- and second-trimester spontaneous abortions.

This study assessed data collected for the California Teachers Study from 1995 to 2004, a nine-year period, on over 100,000 “current, recent, and retired female public school teachers and administrators.”

- **Induced abortion.** The Henderson study found no significant influence for induced abortion for either parous or nulliparous women when assessed generally or when assessed by number of induced abortions procured, by age at first induced abortion, or by year of first induced abortion.
- **Spontaneous abortion.** The Henderson study found no significant influence for spontaneous abortion for either parous or nulliparous women when assessed generally, by number of spontaneous abortions, or by age at first spontaneous abortion.
- **Unsuitable comparisons.** However (as is evident by the results described above), rather than comparing all cohorts against women with only complete, full-term pregnancies, the authors of the Henderson study constructed two comparisons: one of nulliparous women and one of parous women. In the first, nulliparous women who had never been pregnant were compared to nulliparous women who had had abortions. This comparison is inappropriate. The breast cancer risk of the nulliparous women who have had abortions is less stark when compared to nulliparous women who have never been pregnant (rather than to the appropriate reference group); hence, the increased risk contributed by abortion is muted.

¹⁰⁵ 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.

- **Unsophisticated analysis of induced abortion.** The second comparison was of parous women who had had only full-term pregnancies and parous women who had procured abortions. This is a correct comparison, but the critical data on the sequence of births and abortions among the parous and aborting cohort are missing. (It may exist in the raw dataset, but it was not analyzed in the written journal article.) As noted earlier, the sequence of these reproductive events is extremely important in establishing the breast cancer risk abortion contributes.
- **Health or survivor bias.** Though the total number of women sampled who had an induced abortion is reported in the study, the time at which they had an abortion is not. All data regarding pregnancy history were collected by the time of the baseline questionnaire, meaning that all women were followed for at least nine years after an induced or spontaneous abortion. However, the youngest of the women could have obtained abortions 15 years before the time of the baseline questionnaire (and abortions procured by older women could be even further back in their reproductive pasts).¹⁰⁶ Note that breast cancers resulting from induced abortions will likely become detectable about a decade to 14 years after the abortion is procured. Furthermore, women with a previous or unknown history of breast cancer were excluded from the studied cohort. Survivor or health bias was thus introduced into the study. This problem is all the greater because whereas a total of 3,325 women were diagnosed with breast cancer during the study, 6,319 women—nearly twice as many—with previous history of breast cancer or whose breast cancer history was undetermined were excluded. Finally, like the Michels study, this study excluded the development of ductal *in situ* breast cancers. No explanation was offered for its exclusion. The authors would have done better to select a cohort with no reproductive events before a given date and to examine their cancer development or non-development thereafter, because by including only women with abortion history who were breast cancer-free until the baseline questionnaire, the authors biased their study's results away from abortion-breast cancer linkage.
- **Data not randomized.** Like the Michels study, the Henderson study's population sample is biased. Their sample is mostly white, and (as noted earlier) the IQ of teachers (i.e., of women with at least a Bachelor's degree) is not representative of the general population. Henderson et al. control for race, but they do not control for education; hence, their results are not generalizable. The authors admit as much in their discussion: "The current results, may have limited generalizability. In addition to limited racial/ethnic diversity relative to the general female population of the United States, the CTS is characterized

¹⁰⁶ The median ages of the various cohorts at the time of the baseline questionnaire ranged from 45.3 to 53.8, with standard deviations ranging from 11.9 to 14.4 years.

by a higher level of education and associated characteristics such as later age at first full-term pregnancy.”

- **No distinction between first- and second-trimester spontaneous abortions.** Finally, the Henderson study fails to distinguish between first- and second-trimester spontaneous abortions. This is a shortcoming. The presence of these biases are in line with an attitude expressed by one of the authors, Leslie Bernstein, in an interview in 2003, “I don’t want the issue relating induced abortion to breast cancer risk to be part of the mix of the discussion of induced abortion, its legality, its continued availability.”¹⁰⁷

As an aside, the Henderson study states in its introduction that no studies that collected prospective data showed a link between abortion and breast cancer. In stating this, it disregarded the Howe study, a record linkage study (that is, a study that links medical records) not subject to the recall bias or reporting bias they suggest taints retrospective studies, that showed a significantly increased risk of breast cancer with induced abortion.¹⁰⁸

7. 2013 Braüner study

A 2013 study by Braüner et al. of parous Danish women¹⁰⁹ found no association between induced abortion and breast cancer risk. This prospective study included women identified through the Danish Diet, Cancer and Health study and assessed the effect of induced abortion with respect to the timing of one’s first full-term pregnancy. However, the study has several weaknesses that render it insignificant.

Though this study is superior to other prospective studies in its methods and comparisons, it is rendered useless by the massive bias introduced by the 38 percent response rate to the Diet, Cancer and Health study, as well as a possible lack of generalizability. It is also marked by survivor or health bias in concert with the age of its cohort, by failing to assess the effect of repeated induced abortions, by including only parous women, and by failing to include adequate controls for other risk factors for breast cancer.

- **Induced abortion.** The Braüner study found no significant influence for induced abortion, generally or before or after a live birth, on breast cancer risk.
- **Unsuitable data source.** The study relied on data from the Diet, Cancer and Health study, which invited 79,729 women to participate. A mere 29,875 women accepted the invitation. Approximately 63 percent of participants chose to decline the invitation to participate in this study.

¹⁰⁷ R.M. Lowe, “NCI Scientific Panel Concludes Abortion Has No Impact on Breast Cancer Risk,” CancerPage.com; <http://www.cancerpage.com/news/article.asp?id=5601> (accessed January 7, 2013).

¹⁰⁸ Holly L. Howe, Ruby T. Senie, Helen Bzduch, and Peter Herzfeld, “Early Abortion and Breast Cancer Risk Among Women Under Age 40,” *International Journal of Epidemiology* 18 (1989): 300-304. See section entitled “Epidemiological studies that support an induced abortion-breast cancer link.”

¹⁰⁹ 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 Obstetrica et Gynecologica Scandinavica* 92, issue 6 (2013): 700-705.

- **Data not randomized.** The authors also note that “[t]he rationale behind the study design was to include highly motivated people, and consequently secure a high participation in the follow-up investigation. . . . Not unlike other follow-up studies, the women who refused to participate had a low socioeconomic status. The participation was greater among women with a high income and a higher education compared to other Danish women (13). The incidence of breast cancer was also higher in the study population.”¹¹⁰ Despite including controls for education, Braüner et al. include no controls for socioeconomic status, and as Patrick Carroll states in his letter to the editor of the journal in which the Braüner study appears, the authors do not note *how much higher* was the incidence of breast cancer in the study population.¹¹¹ Hence, as the sample was not representative of the general Danish population, its results may be imperfectly generalizable to the general Danish population.
- **Health or survivor bias.** Second, the study appears to be affected by the same sort of survivor bias or health bias that affects so many other studies. The authors excluded 337 women from their cohort who had previously experienced cancer. Though likely not all 337 cancer incidences were breast cancer cases, the importance of these cases’ exclusion becomes clear when one considers that the Braüner study only assessed 1,215 cases of breast cancer. Hence, up to 22 percent of breast cancers diagnosed within the cohort may have been excluded. This is a serious bias that would skew the results away from linkage of induced abortion and breast cancer.

The error becomes all the more egregious in light of the age of the cohort in the Braüner study. The women included were aged 50 to 65 at the time of their inclusion in the Diet, Cancer and Health study between 1993 and 1997, and they were followed for an average of 12 years thereafter. Given that breast cancer from an induced abortion will most likely show up around a decade to 14 years thereafter, it is likely that only abortions procured about 10 to 14 years before the baseline period, when the women sampled were between the ages of about 36 and 55, would produce breast cancer detectable during the study period. However, females’ reproductive years are (approximately) between the ages of 15 and 45, and as demand for induced abortion among women over

¹¹⁰ 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 Obstetrica et Gynecologica Scandinavica* 92, issue 6 (2013): 700-705.

¹¹¹ Patrick Carroll, “Induced abortion and breast cancer,” *Acta Obstetrica et Gynecologica Scandinavica* (2013).

the age of 40 is relatively low,¹¹² it may be that those breast cancers occurring as a result of earlier induced abortion were excluded. The breast cancers excluded may have been the only breast cancers caused by abortions—and thus *precisely* the breast cancers of interest to the study.

- **Too-simple analysis of induced abortion.** Third, the study does not assess the effect of repeated induced abortion.
- **Restriction to parous women.** Fourth, though the study utilizes the correct reference group (parous women with no abortion history), it restricts its analysis to parous women. Though the assessment of the effects of induced abortion on parous women is useful, we are also concerned with the effect of induced abortion on nulliparous women, who never experience the protective benefit of full-term pregnancy.
- **Omitted variable bias.** Finally, the study neglects to include some important variables in its analysis. Its model is incomplete and does not include family history of breast cancer or age at menarche, for example, in its regressions. The Braüner study also does not include spontaneous abortion in its analyses, let alone distinguish between first- and second-trimester spontaneous abortions.

C. Ecological Epidemiological Studies That Support an Induced Abortion-Breast Cancer Link, With Analyses

Ecological epidemiological studies use gross vital-statistic-like data, such as the incidence of breast cancer or abortions in a county, state, or country. Patients are not interviewed, and hospital records are not examined. Two ecological epidemiological studies, one in the USSR and one in Western Europe, show a strong association between induced abortion and breast cancer.

1. 1989 Remmenick study

Larissa Remennick's 1989 study of breast and cervical cancers in the USSR showed a "consistent association between abortion rates...and incidence of both breast and cervical cancers."¹¹³ The author notes that abortions exceeded live births in the years following abortion's legalization in 1955, due to the procedure's use as the nation's primary means of birth control.

Remmenick found that, overall, the induced abortion rate was the fourth-ranked variable in determining age-adjusted breast cancer incidence (after cumulative fertility

¹¹² A mere 3 percent of abortions in the U.S. in 2008 were procured by women aged 40 or older. Whereas 16 percent of abortions in Denmark in 2010 were procured by women under age 20, 43 percent by women aged 20 to 29, and 33 percent by women aged 30 to 39, only 7 percent of abortions were procured by women 40 or older. See Gilda Sedgh, Akinrinola Bankole, Susheela Singh, and Michelle Eilers, "Legal Abortion Levels and Trends By Woman's Age at Termination," *International Perspectives on Sexual and Reproductive Health* 38, no. 3 (September 2012): 144; <http://www.guttmacher.org/pubs/journals/3814312.pdf> (accessed July 5, 2013).

¹¹³ 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.

rate, early marriage prevalence, and early age at first birth prevalence). This finding is remarkable given the small percentage of women aborting in primigravidas (that is, aborting their first pregnancies) and given that all induced abortions here are aggregated and not parsed out (e.g., by their timing related to first full-term pregnancy). However, the very fact that a small percentage of women aborted in primigravidas provides a clear picture of the potential effects of repeated abortions, even when they take place after full-term pregnancy.

2. 2007 Carroll study

In 2007, actuary Patrick Carroll found,¹¹⁴ with an empirical model that he built from English and Welsh data, that of the four reproductive risk factors he tested, the greatest predictor of future breast cancer incidence was a nation's abortion rate. Nulliparous abortions, in particular, were significant in determining breast cancer rates.

Carroll also found that falling fertility affected the incidence of breast cancer. Using national abortion, fertility, and breast cancer registries, Carroll made predictions regarding breast cancer rates in nine European countries (England, Wales, Scotland, Northern Ireland, the Irish Republic, Sweden, the Czech Republic, Finland, and Denmark).

D. Epidemiological Studies That Support an Induced Abortion-Breast Cancer Link, With Analyses

The following series of studies show some relationship between induced abortion and breast cancer. These 19 studies occur across diverse countries and cultures—from Japan and China, to Iran and Armenia, to Germany and the United States. They are organized chronologically and (loosely) in order of increasing statistical and methodological sophistication.

1. *Early, developmental, suggestive research*

a) 1957 Segi study

The first epidemiologic study examining breast cancer and abortion was published in 1957 in Japan.¹¹⁵ As the study is written—with data broken down by number of pregnancy outcomes (e.g., induced abortion, miscarriage), rather than by women experiencing these outcomes—the results are not comparable to those of other studies. However, in his 1996 meta-analysis, Joel Brind uses other Japanese studies to approximate the average number of induced abortions to which each woman with induced abortion history was exposed.

As Brind notes, the Segi study only includes parous women, and the control population is “slightly older than the patient population,” but by his estimation, the study

¹¹⁴ 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.

¹¹⁵ 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.

shows evidence of a statistically significant increase in the risk of breast cancer among women with a history of induced abortion.¹¹⁶

b) 1981 Pike study

The first U.S. study of abortion and breast cancer in 1981,¹¹⁷ which analyzed the history of a total sample of 435 Los Angeles County women, also suggested an increased (though perhaps not significant) risk of breast cancer with induced abortion.

This study is insufficiently randomized, has a small sample, is based on interviews conducted over the telephone, is marked by sampling bias and survivor or health bias, and may suffer from reporting difficulties surrounding abortion law change. Its cases and controls differ across risk factors other than induced abortion, several possible breast cancer risk factors are left out of its analyses, and its analyses are not multiple regressions. Additionally, its analysis does not distinguish between induced and spontaneous abortion. Many of these are a consequence of its early, exploratory nature; regardless, this study was a very important step in the development of the field of induced abortion and breast cancer.

The case-control study included 163 white breast cancer patients diagnosed, before the age of 33, between July 1972 and December 1978 and identified through the University of Southern California Cancer Surveillance Program. These cases were matched with 153 neighborhood controls and 119 friend controls.

- **Small sample, limited generalizability, unsuitable data collection means.** Pike's sample is quite small. That all participants were white would limit the generalizability of the study's findings. Additionally, the interview's administration over the telephone could diminish any influence of induced abortion through underreporting.
- **Health or survivor bias.** Deceased cases were excluded, and this survivor bias may have weakened the demonstrated effect of induced abortion. Furthermore, "controls had to be malignancy-free," and this health bias may have skewed the demonstrated effect of induced abortion.¹¹⁸ However, the restriction of the

¹¹⁶ Joel Brind, Vernon M. Chinchilli, Walter B. Severs, and Joan Summy-Long, "Induced Abortion as an Independent Risk Factor for Breast Cancer: A Comprehensive Review and Meta-Analysis," *Journal of Epidemiology and Community Health* 50, no. 5 (1996): 483-484.

¹¹⁷ 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.

¹¹⁸ If the correlation between induced abortion and breast cancer exists, a univariate bias (throwing out malignant people in the control group) throws out aborting people (in the control group). Because the control group has even fewer abortions now (in proportion to the levels cases exhibit), the statistic shows an even stronger correlation (more effect) between induced abortion and breast cancer: Throwing out malignant controls would bias the effect of induced abortion upward.

If there is no correlation between induced abortion and breast cancer, throwing out malignant women would not throw out any extra aborting women (in proportion) in the control group. Abortng women (not being any more likely to be malignant than the other controls) are dropped with the same frequency as the other controls: Throwing out malignant controls would not bias the analysis.

study to women under 33 reduces the likelihood that a very early abortion resulting in breast cancer would eliminate women diagnosed with breast cancer before the start of the study, a problem we discuss in detail above.

- **Reporting difficulty around abortion law change.** Following the signing of the 1967 Therapeutic Abortion Act,¹¹⁹ the data seem to show that the incidence of induced abortion increased markedly.¹²⁰ Because of the time frame of this study, and because of the eight to 10 years required for the development of detectable breast cancers, it is likely that some fraction of the women with detectable cases of breast cancer in this sample had legally procured abortions and some women had illegally procured abortions. (All women were residing in Los Angeles County at the time of their diagnosis, but it may be that some did not live in California at the time of their abortion or procured their abortion elsewhere.) It would have been interesting to assess the timing of the induced abortions alongside corresponding breast cancer diagnoses.
- **Lack of multivariate regressions, neglect of potential breast cancer risk factors.** It is clear that the case and control groups differ significantly across risk factors other than induced abortion. Also, the authors appear not to have conducted multivariate regressions or applied multiple controls to their analysis of induced abortion (or of other risk factors). Some potential breast cancer risk factors appear to have been left out of their analysis. This is likely a consequence of the study's early date. Lacking multiple controls, this study may attribute the influence of such variables as lower or late parity (or both) or use of oral contraception on breast cancer to induced abortion. Regardless, as we note above, this study—like other such early, developmental, suggestive studies—was a step in the development of the field of induced abortion and breast cancer.
- **Pregnancy outcomes.** The authors found a significant increase in breast cancer risk among women who experience an “early” abortion (i.e., an abortion before 12 weeks' gestation) prior to their first full-term pregnancy. They do not distinguish between induced and spontaneous abortion; 11 of the 24 abortions among cases and eight of 17 abortions among the controls were induced. Those women who subsequently had a full-term pregnancy saw a somewhat reduced risk of breast cancer, though the authors do not specify how precisely this risk reduction is determinable. The authors also note that

¹¹⁹ Planned Parenthood Affiliates of California Action Funds, “Issues: History of Abortion Law in California,” Planned Parenthood Action Funds in California; <http://www.ppactionca.org/issues/abortion.html> (accessed April 18, 2013). The site notes that the 1967 Therapeutic Abortion Act “[m]ade abortion legal if authorized by a hospital committee that finds the pregnancy will gravely impair a woman's physical or mental health, or where a local district attorney or court finds probable cause to believe the pregnancy resulted from rape or incest.”

¹²⁰ Wm. Robert Johnston, “Historical abortion statistics, California (USA),” Abortion statistics and other data--Johnston's Archive, November 21, 2012; <http://www.johnstonsarchive.net/policy/abortion/usa/ab-usa-CA.html> (accessed April 18, 2013).

abortions after first full-term pregnancy or after three months' gestation did not appear to increase one's risk of breast cancer. Pike et al. do not assess the influence of induced abortion history, in general, or the influence of repeated induced abortions or gestational period of or maternal age at induced abortion.

- **Full-term pregnancy and age at first full-term pregnancy.** Having a full-term pregnancy and age at first full-term pregnancy (as a trend) were not found to significantly affect the risk of breast cancer.
- **Various risk factors.** History of breast cancer in one's mother or sister, history of benign breast disease, and earlier age at menarche (as a trend—younger than 12 versus at age 12 or at age 13 or older) were all found to significantly increase risk of breast cancer.
- **Oral contraceptive use duration, timing, and interaction with other factors.** As a trend, increasing duration of oral contraceptive use was shown to have a positive and statistically significant influence on breast cancer risk. Versus never using oral contraception, using oral contraception for up to four years contributed to a slight increase in risk, and use for more than four years contributed to a larger increase in risk.

As a trend, oral contraceptive use prior to first full-term pregnancy for up to four years contributed to a very slight increase in risk. Using oral contraception prior to first full-term pregnancy for four to eight years, or for eight years or longer, contributed to ever more marked increases in breast cancer risk. No clear trend was detectable in an analysis of duration of oral contraceptive use after first full-term pregnancy (this analysis was conducted among parous women only).

Oral contraceptive use before first full-term pregnancy appeared to have a greater effect on breast cancer risk in concert with benign breast disease, though the number of cases and controls considered is very small and the authors do not show how precisely determinable is the risk.

- **Induced abortion.** In his 1996 meta-analysis, Joel Brind distinguishes between induced and spontaneous abortions in the 1981 Pike study and found that, unadjusted for other factors, the impact of induced abortion prior to first full-term pregnancy had a positive but slightly reduced and statistically insignificant influence on breast cancer risk.¹²¹

c) 1982 Nishiyama study

Brind notes in his 1996 meta-analysis¹²² that the 1982 Nishiyama study,¹²³ which was written in Japanese, "compared 767 radical mastectomy patients from a single prefecture in Japan with an equal number of age matched, normal controls identified

¹²¹ Joel Brind, Vernon M. Chinchilli, Walter B. Severs, and Joan Summy-Long, "Induced Abortion as an Independent Risk Factor for Breast Cancer: A Comprehensive Review and Meta-Analysis," *Journal of Epidemiology and Community Health* 50, no. 5 (1996): 483-484.

¹²² *Id.* at 484.

¹²³ F. Nishiyama, "The Epidemiology of Breast Cancer in Tokushima Prefecture," *Shikoku Ichi* 38 (1982): 333-343.

through a mass breast cancer screening programme.” According to Brind’s report, the Nishiyama study showed induced abortion to have a positive, significant influence on breast cancer risk.

2. Early epidemiological-statistical control studies

d) 1988 Ewertz and Duffy study

In 1988, Ewertz and Duffy¹²⁴ found that having one induced abortion contributed to increased risk of breast cancer among Danish women. This study is marked by health and survivor bias, its analyses neglect some breast cancer risk factors and are not multivariate regressions, it may be marked by difficulties related to reporting and induced abortion law changes, and in some cases it does not distinguish between induced and spontaneous abortion (e.g., when assessing the influence of breast cancer with respect to the timing of one’s first full-term pregnancy). Regardless, as in the case of the Pike study, Ewertz and Duffy’s study was a step in the development of the field of induced abortion and breast cancer.

The authors conducted a study comprised of 1,486 cases and 1,336 controls residing in Denmark. The cases were women under 70 years of age who had been diagnosed with invasive breast cancer or carcinoma *in situ* between March 1983 and March 1984, who were identified through the Danish Breast Cancer Co-operative Group and the Danish Cancer Registry. Controls were identified through the Danish Central Population Registry.

- **Health or survivor bias.** The Ewertz and Duffy study is marked by health and survivor bias. Cases and controls with previous history of breast cancer were excluded.¹²⁵ Some cases died, and some were not notified in time to participate in the study, so they were excluded as well. Most women in the Ewertz and Duffy study—around 90 percent of those who responded to the invitation to participate in the questionnaire—were diagnosed after age 40: around one third were diagnosed in their 40s, around one third were diagnosed in their 50s, and around one third were diagnosed in their 60s. If breast cancer resulting from an induced abortion is most likely to manifest itself around a decade to 14 years after the abortion’s being procured, then the exclusion of

¹²⁴ 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.

¹²⁵ If the correlation between induced abortion and breast cancer exists, a univariate bias (throwing out controls with a previous history of breast cancer) throws out aborting people (in the control group). Because the control group has even fewer abortions now (in proportion to the levels cases exhibit), the statistic shows an even stronger correlation (more effect) between induced abortion and breast cancer: Throwing out controls with a previous history of breast cancer would bias the effect of induced abortion upward.

If there is no correlation between induced abortion and breast cancer, throwing out controls with a previous history of breast cancer would not throw out any extra aborting women (in proportion) in the control group. Abortng women (not being any more likely to have had breast cancer than the other controls) are dropped with the same frequency as the other controls: Throwing out controls with a previous history of breast cancer would not bias the analysis.

women with a previous history of breast cancer likely eliminated all women whose breast cancer was the result of an induced abortion. These survivor or health biases could have skewed the study's results away from induced abortion-breast cancer linkage.

- **Reporting difficulty around abortion law change.** The study also may be marked by difficulties related to abortion law changes. As we note in our analysis of Melbye et al., induced abortion law was liberalized in Denmark in 1973 (around a decade before the breast cancers included in this study were diagnosed). Many women diagnosed with breast cancer in the Ewertz and Duffy study were well past their reproductive years and, hence, past any “need” for induced abortion at the time of its legalization. These women may have procured illegal abortions and may be reluctant to report them for the purposes of the study. Their classification as non-aborting may have skewed the data away from induced abortion-breast cancer linkage.
- **Lack of multivariate regressions.** The authors analyze and control for differences between age at diagnosis, marital status, and residence between cases and controls, but their analyses are not multivariate regressions. Lacking multiple controls, this study may attribute the influence of other variables on breast cancer to induced abortion. Their various analyses include variables for age at menarche, age at natural menopause, menopausal status, whether one's first pregnancy was incomplete, number of full-term pregnancies, age at first full-term pregnancy, type (e.g., spontaneous or induced) and timing of abortion (relative to first full-term pregnancy), type of cancer contracted, and oral contraceptive use.
- **Pregnancy outcomes.** In their general model, Ewertz and Duffy adjust their risk ratios for age at breast cancer diagnosis and place of residence. Relative to one's first pregnancy being a full-term pregnancy (by which Ewertz et al. mean a pregnancy lasting 28 weeks or longer), “early termination” of one's first pregnancy positively and significantly influenced one's risk of breast cancer. Never experiencing pregnancy also positively and significantly increased one's risk of breast cancer.

Relative to women with no induced or spontaneous abortions (whose first pregnancy was carried to term), among women with no full-term pregnancies, experiencing any type of abortion (spontaneous or induced) was found to increase one's risk of breast cancer.

However, no significant effect was found based on the timing of abortion relative to one's first full-term pregnancy. This may be because, though the authors distinguish abortions as taking place either before or after first full-term pregnancy and based on the trimester in which they take place, they fail to distinguish between spontaneous and induced abortions. We assume they have chosen not to do so because the resulting categories would be too small

for any “signal” to be perceptible above fluctuations (in responses) from other sources of error.

- **Too-simple analysis of abortion.** Ewertz and Duffy did not assess the influence of maternal age on either general abortion or abortions broken out by type (induced and spontaneous) on breast cancer risk.
- **Induced abortion.** When stratifying by type of abortion, the authors found that one induced abortion among women with no full-term pregnancies had a positive, significant influence on breast cancer risk, relative to women with no induced or spontaneous abortions (i.e., those women whose first pregnancy was carried to term). That a significant effect was detected is all the more remarkable considering that, compared to 1,142 cases and 1,116 controls with no abortion history, only 13 cases and three controls had induced abortion history.
- **Spontaneous abortion.** No significant effect was found for first-trimester spontaneous abortions or for second-trimester spontaneous abortions. Though the latter contradicts our hypothesis, it may be merely due to the fact that only three cases and two controls had had a second trimester spontaneous abortion. Ewertz and Duffy chose the correct comparison group for their aborting cohorts—women with no abortions and at least one full-term pregnancy.
- **Number of full-term pregnancies.** Relative to having only one full-term pregnancy, having four or more full-term pregnancies was significantly protective against breast cancer. (One’s first pregnancy continuing to term, we have already seen, is protective, relative to early termination or never being pregnant. Having four or more full-term pregnancies is not merely protective, relative to nulliparity; it is protective relative to having one full-term pregnancy!) As a trend, increasing number of full-term pregnancies was negatively correlated with breast cancer risk, and this trend was precisely determinable. The authors would have done well to use nulliparity as the reference category in their analysis of number of full-term pregnancies. As their regression tables are currently designed, the benefits of increasing numbers of full-term pregnancies are less than clear.
- **Age at first full-term pregnancy.** No particular age at first pregnancy was found to be significantly protective, and as a trend, age at first pregnancy was not found to have any significant association with breast cancer risk. No significant association was found between age at first full-term pregnancy and type of breast cancer (ductal or lobular) contracted.
- **Number of full-term pregnancies and age at first full-term pregnancy.** Among women with two full-term pregnancies, experiencing first full-term pregnancy between ages 20 and 24, between ages 25 and 29, and at age 30 or older provided increasingly *greater* protection against breast cancer, relative to experiencing first full-term pregnancy prior to age 20. As a trend, increasing age at first full-term pregnancy among women with two full-term pregnancies was

associated with decreased breast cancer risk. No significant associations were found among women with one, three, or four or more full-term pregnancies.

Among women whose first full-term pregnancy was between ages 20 and 24, an increasing number of full-term pregnancies was associated with decreased breast cancer risk, as a trend. No significant effect was found for an increasing number of full-term pregnancies among women whose first full-term pregnancy occurred prior to age 20, between ages 25 and 29, or at or after age 30.

When adjusted for age at first full-term pregnancy, having four or more full-term pregnancies was shown to be even more protective than in the general model, relative to having one full-term pregnancy. As a trend, an increasing number of full-term pregnancies (adjusted for age at first full-term pregnancy) was associated with reduced breast cancer risk, and this trend was precisely determinable.

- **Number of full-term pregnancies and age at breast cancer diagnosis.** When analyzed in concert with age at breast cancer diagnosis, any number of full-term pregnancies was protective against breast cancer, relative to nulliparity. This was especially true among women diagnosed between ages 50 and 59.
- **Age at first full-term pregnancy and age at breast cancer diagnosis.** The risk associated with increasing age at first full-term pregnancy increased among women diagnosed before age 60 but decreased among those diagnosed after age 60.
- **Number of full-term pregnancies, age at first full-term pregnancy, and diagnosis with breast cancer before or after age 60.** The authors tentatively suggest that whereas age at first full-term pregnancy is of more importance than parity among women diagnosed before age 60, parity may be of more importance than age at first full-term pregnancy thereafter. Interpreted: One's age at first full-term pregnancy is determined at least in part by procured abortions and use of contraception. Any effect of these factors can only persist for a decade to 14 years or so after exposure.¹²⁶ Hence, age at first full-term pregnancy is important in determining breast cancer risk prior to age 60: the effects of abortion and hormonal contraception are unlikely to persist long after the reproductive years have ended and these factors are no longer active. After age 60, these factors are no longer active. The body is susceptible to other environmental factors, and one's susceptibility is determined by parity

¹²⁶ Dolle et al. show a positive and significant increase in breast cancer risk in women who used oral contraception one to fewer than five years in the past and 10 to fewer than 15 years in the past. Current oral contraceptive use and use one to fewer than five, five to fewer than 10, and 10 to fewer than 15 years in the past was shown to have a positive and significant influence on triple-negative breast cancer risk. However, for no breast cancer category assessed was any effect was detected for oral contraceptive use 15 or more years in the past. See Jessica M. Dolle, Janet R. Daling, Emily White, Louise A. Brinton, David R. Doody, Peggy L. Porter, and Kathleen E. Malone, "Risk Factors for Triple-Negative Breast Cancer in Women Under the Age of 45 Years," *Cancer Epidemiology, Biomarkers and Prevention* 18, no. 4 (2009): 1159. See also Appendix D for further explanation on breast cancer's manifestation.

(i.e., how much protection has been built up in the body), which is less directly affected by use of oral contraceptives and induced abortion. However, the authors note that “[f]ormal statistical significance was...barely reached in these analyses, so interpretation must be cautious.”

- **Age at menarche.** Ewertz and Duffy find menarche at 15 years of age or 16 years of age or older to be significantly protective against (i.e., to be negatively correlated with) breast cancer, relative to menarche prior to age 13. As a trend, increasing age at menarche was negatively associated with breast cancer risk, and this trend was very precisely determinable.
- **Menopausal status and age at menopause.** Being postmenopausal had a significantly negative influence on breast cancer risk. Having commenced menopause between the ages of 50 and 55 also had a significant and positive influence on breast cancer. As a trend, increasing age at menopause was associated with increased risk of breast cancer, and this trend was precisely determinable.
- **Various risk factors.** The general model does not include variables for oral contraceptive use or smoking. This is a weakness and a consequence of the study's early, exploratory nature.

e) 1989 Howe study

Howe et al.¹²⁷ found in 1989 that induced abortions before 20 weeks' gestation had a positive, significant influence on breast cancer risk. The study is flawed by a lack of data on parity for women who did not experience an induced or spontaneous abortion, short time period between abortion and breast cancer diagnosis, possible reporting difficulties surrounding abortion law change, underreporting and inconsistent distinguishing between induced and spontaneous abortions, a lack of distinction between first- and second-trimester spontaneous abortions, an apparent lack of multiple controls, and a small model. However, the authors restrict their analysis to women under 40 at the time of their diagnosis, an effort that would have protected their analysis to some degree from health or survivor bias, and their model is a record linkage model, eliminating any possibility that the “recall bias” or differential “reporting bias” between cases and controls that some assert undermines case-control studies could taint their work.

The authors identified 1,451 women with breast cancer using public records in New York State (excluding women in New York City), which legalized abortion on demand up to 24 weeks in 1970. One control was matched to each case using New York State driver's license records. All women were matched to public health records on incidence of fetal death, whether a fetal death occurred through spontaneous abortion or induced abortion, between 1971 and 1980. (Fetal deaths after breast cancer diagnosis were not included.) These records also included information on previous pregnancies and their outcomes. The study's sample was confined to pregnancies lasting 20 weeks or fewer.

¹²⁷ Holly L. Howe, Ruby T. Senie, Helen Bzduch, and Peter Herzfeld, “Early Abortion and Breast Cancer Risk Among Women Under Age 40,” *International Journal of Epidemiology* 18 (1989): 300-304.

- **Lack of data on parity.** One hundred cases and 63 controls—not a large sample—were found to have had abortions prior to 20 weeks' gestation. Data regarding pregnancies and their outcomes among women who did *not* have a reported fetal death were not available, and this may have affected the risk of abortion as it is demonstrated in the study.
- **Insufficient follow-up time.** Another shortcoming that affects the study is the lack of time between fetal death and breast cancer diagnosis. As noted earlier, all diagnoses took place between 1976 and 1980, and all fetal deaths were recorded between 1971 and 1980. Though it is unlikely that a spurious association between abortion and breast cancer would have been created by a lack of follow-up time after fetal death, this dearth of time may have weakened induced abortion's demonstrated influence on breast cancer.
- **Reporting difficulty around abortion law change.** Furthermore, though (as the authors note) abortion was available on demand as of July 1970 in New York State, many of the respondents' reproductive years would have taken place prior to the law's liberalization. This may also have weakened any effect due to induced abortion.
- **Incomplete distinction between induced and spontaneous abortions.** Finally, Howe et al. note "some evidence for underreporting and inconsistent reporting of early pregnancy terminations." For example, some women did not report recorded induced abortions, and some women had reported their abortions were spontaneous when they were recorded as induced. The authors indicate (though they do not demonstrate) that the incidence of this underreporting and inconsistent reporting was approximately even across both cases and controls. However, it is possible that the reporting of induced abortions as spontaneous abortions in case-control studies could skew a study's findings away from induced abortion-breast cancer linkage and show some small positive effect for spontaneous abortions. Additionally, some analyses in the study do not distinguish between induced and spontaneous abortions; these analyses are thus of limited use to the reader.
- **Record linkage model (no possible "recall bias").** That the study's material proceeds from linked records, however, is a definite strength. Some critics of case-control studies argue that controls may underreport their abortions; the record linkage model (that is, a model that links medical records) employed by Howe et al. eliminates the likelihood that women would underreport abortions based on their status as a case or a control, because at the time the report of fetal death was taken, the cases had not yet been diagnosed with breast cancer.
- **An attempted reduction of health or survivor bias.** All cases were under age 40 at their diagnosis, which took place between 1976 and 1980. This restriction to women still in their reproductive years may have reduced health or survivor bias in their study.

- **Lack of multivariate regressions.** The authors did not build a large model. Howe et al. appear to have assessed the differences between aborting women and the general sample regarding demographic (age at diagnosis, marital status, education, race) and other factors, but not to have thusly adjusted the odds ratios associated with abortion. These factors include age at first pregnancy (between women who did and did not carry their first pregnancy to term), age at first live birth (between cases and controls), age at first “pregnancy interruption” (between cases and controls), average total number of pregnancies (between cases and controls), and average length of gestation (between cases and controls). Their analyses appear not to be multivariate analyses. Lacking multiple controls, this study may attribute the influence of other variables on breast cancer to induced abortion. Howe et al. also neglect to assess the differences between cases and controls on some breast cancer risk factors: Among other factors, their analysis neglects oral contraceptive use, smoking, number of full-term pregnancies, age at menopause, or menopausal status (though, because all women studied were diagnosed prior to age 40, these last two variables are of less concern).
- **Pregnancy outcomes.** In their initial analysis of the effects of abortion before 20 weeks’ gestation (spontaneous and induced abortions combined), they find no effect when a first pregnancy ends in abortion. Howe et al. find (combined) abortions after a first pregnancy to have a significant, positive influence on breast cancer risk. When all pregnancies ending in abortion are combined, they are found, as well, to have a significant, positive influence on breast cancer risk.

When spontaneous and induced abortions are distinguished, no significant effect is found for spontaneous abortions or among women who had both spontaneous and induced abortions. Induced abortions were found to have a positive, significant influence on breast cancer risk.
- **Too-simple analysis of induced abortion, no distinction between first- and second-trimester spontaneous abortions.** Howe et al. do not assess the influence of gestational age or maternal age at the time of induced abortion or spontaneous abortion. They also do not distinguish between first- and second-trimester spontaneous abortions.
- **Repeated incomplete pregnancies.** Howe et al. also note that they find “a history of repeated interrupted pregnancies with no intervening livebirths” to have a positive and significant influence on breast cancer risk. This is stated in text and not demonstrated in a table, but the odds ratio and confidence interval are stated. This analysis includes both induced and spontaneous abortions.

f) 1993 Laing study

Laing et al.'s study of breast cancer in African-American women in Washington, D.C., was released in 1993.¹²⁸ The study cited a need for specific research into breast cancer in black women because of an uptick in breast cancer incidence among under-40 black women and an increase in breast cancer mortality among black women younger than 50. The study found induced abortion had a positive, significant influence on breast cancer risk among women diagnosed at age 50 or older and a positive, marginally significant influence among women diagnosed between the ages of 41 and 49. This study is of limited generalizability (because of its exclusion to African-American women), is marked by health bias, excludes important data on various important breast cancer risk factors (and thereby risks introducing omitted variable bias), contains possible reporting difficulties surrounding abortion law changes, fails to distinguish between first- and second-trimester spontaneous abortions, and conducts an unsophisticated analysis of induced abortions.

- **Limited generalizability, health or survivor bias.** The study included 503 African-American cases identified through Howard University Hospital in Washington, D.C., between 1978 and 1987. Five hundred thirty-nine African-American age-matched controls who presented with “nonmalignant conditions” at the same hospital were also included in the study. This restriction of the study to African-American women limits its generalizability, and the exclusion of controls with breast cancer is a health bias that could skew the results of their analysis away from linkage between induced abortion and breast cancer.
- **Exclusion of some potential breast cancer risk factors.** Laing et al. identify the differences between their cases and controls and analyze them in a fairly thorough model. They do not include data on age at first full-term pregnancy, education, smoking, or alcohol use, and therefore risk introducing omitted variable bias, but they do control for number of induced abortions, number of spontaneous abortions, parity, oral contraceptive use, lactation, age at menarche, menopausal status, and marital status.
- **Induced abortion.** Women aged 50 or older at their breast cancer diagnosis who had induced abortion history had a significantly increased risk of breast cancer, relative to women with no history of induced or spontaneous abortion. Women aged 41 to 49 at their breast cancer diagnosis who had induced abortion history had a marginally significantly increased risk of breast cancer. No significant effect was detected with induced abortion among women diagnosed at age 40 or younger.

Laing et al. note evidence of possible underreporting among older controls, which may have shifted the odds ratio associated with

¹²⁸ A.E. Laing, Florence M. Demenais, Rosemary Williams, Grace Kissling, Vivien W. Chen, and George Bonney, “Breast Cancer Risk Factors in African-American Women: The Howard University Tumor Registry Experience,” *Journal of the National Medical Association* 85 (1993): 931-939.

breast cancer and abortion upward. The authors state that whereas consistent numbers of cases report induced abortions across age at diagnosis categories, fewer induced abortions are reported by older controls. They find no such shift in spontaneous abortion incidence.

The assertion Laing et al. make is unnecessary for explaining the pattern they see in their data. It is clear that many more cases than controls reported induced abortions in the cohort of women fifty and older at their breast cancer diagnosis. However, these cases were diagnosed five to 14 years after *Roe v. Wade*, meaning the youngest of the women in this cohort were 36. There would be less demand for abortion in a group so late into their reproductive years. (In 1996, only 10 percent of all abortions in the U.S. were procured by women age 35 or older; this proportion had changed little by 2000 and 2008, in which years about 11 percent of all abortions in the U.S. were procured by women aged 35 or older.¹²⁹) A smaller fraction of women in this cohort took “advantage” of the change legalizing induced abortion. Additionally, women who do choose to procure abortions at this age may be at greater risk of breast cancer than women who procure abortions slightly earlier in their reproductive lives. Thus, there is no need for the hypothesis of reporting bias as it is put forward, but in no way analyzed, by the authors.

- **Unsophisticated analysis of induced abortion.** The authors do not assess the differing effects of induced abortion based on the gestational period at which it was procured, on maternal age at first induced abortion, or on number of induced abortions procured. Though the authors control for parity, they do not assess the effects of induced abortion’s timing relative to first full-term pregnancy, and hence do not examine the effect of parity status *at the time of one’s induced abortion* on one’s vulnerability.
- **Spontaneous abortion.** Women aged 50 or older at their breast cancer diagnosis with a history of spontaneous abortion had a significantly reduced risk of breast cancer, relative to women with no history of induced or spontaneous abortion. No significant effect was found for women aged 41 to 49 or for women 40 years old or younger at their diagnosis with spontaneous abortion history.
- **No distinction between first- and second-trimester spontaneous abortions.** Laing et al. did not distinguish between first- and second-trimester spontaneous abortions.
- **Number of full-term pregnancies.** Relative to women who gave birth to five or more children (the vast majority of these were live births; very few were stillbirths), those who gave birth to three to four children were at a marginally significantly reduced risk of breast cancer, and those who gave birth to one or

¹²⁹ Gilda Sedgh, Akinrinola Bankole, Susheela Singh, and Michelle Eilers, “Legal Abortion Levels and Trends By Woman’s Age at Termination,” *International Perspectives on Sexual and Reproductive Health* 38, no. 3 (September 2012): 144; <http://www.guttmacher.org/pubs/journals/3814312.pdf> (accessed July 5, 2013).

two children were at a significantly reduced risk of breast cancer. No significant association was found with breast cancer for nulliparous women. The authors explain that “[o]ur results might be partly explained by the possibility of a pattern of age at first birth in our data. However, age at first birth was not consistently recorded, so our study could not account for it.”

- **Marital status.** Divorce, separation, and widowhood had a negative (i.e., protective) and significant influence on breast cancer risk, relative to marriage; and singlehood was found to have a marginally significantly protective influence on breast cancer risk. Laing et al. state that the gap in the percentage of never-pregnant women between married and single women is much smaller among black women than among white women and that “[i]t seems possible that single black women may be more similar in their reproductive experience to married black women than is the case with whites.”
- **Age at menarche.** Relative to women who were 15 years old or older at menarche, adjusted odds ratios showed those who were 13 to 14 at menarche to be at a significantly increased risk of breast cancer. No significant associations were found for those who were 11 to 12 or who were 10 years old or younger at menarche.

When women were divided by menopausal status, no significant associations were found regarding age at menarche and breast cancer risk among premenopausal women. Among postmenopausal women, relative to those experiencing menarche at age 15 or older, women who had experienced menarche at 13 to 14 years of age were at a significantly increased risk of breast cancer. Again, no significant associations were found for those who were 11 to 12 or who were 10 years old or younger at menarche.

- **Menopausal status.** No significant associations were found between menopausal status (i.e., being pre- or postmenopausal) and breast cancer risk.
- **Oral contraceptive use.** Analysis of only women born after 1940 showed that ever using oral contraception had a positive and significant influence on breast cancer risk.
- **Breastfeeding.** No significant association was found for lactation history in the multivariate logistic regression, though the authors note that “a large number of cases had missing information on this variable.”
- **Family history of breast cancer.** First-degree (mother or sister) family history of breast cancer, mother-only history of breast cancer, and sister-only history of breast cancer were found to have large, positive, significant influences on breast cancer risk. (These odds ratios are unadjusted “because there were so few controls with a positive first-degree family history.”)

g) 1994 Daling study

Public attention was drawn to the induced abortion-breast cancer link in 1994, when *TIME* magazine covered¹³⁰ a U.S. study by Janet Daling commissioned by the Na-

¹³⁰ Christine Gorman, “Do Abortions Raise the Risk of Breast Cancer?” *TIME*, November 7, 1994, 61.

tional Cancer Institute (NCI).¹³¹ Daling found that having any induced abortion history significantly increased one's breast cancer risk. The study is of limited generalizability and is marked by possible difficulties related to reporting around abortion law changes, as well as health or survivor bias, but it devotes considerable attention to assessing the risk incurred with induced abortion under different circumstances.

The study's cases included white women born after 1944 and residing in King, Pierce, and Snohomish counties, Washington, who were diagnosed with invasive or *in situ* breast cancer between January 1983 and April 1990. The patients were identified through a SEER cancer registry in Washington State. The authors acquired a total sample of 845 cases and 961 controls. Controls were identified through random-digit dialing in King, Pierce, and Snohomish counties.

- **Limited generalizability, survivor or health bias.** That all participants were white would limit the generalizability of the study's findings. The study was confined to women experiencing a first diagnosis of breast cancer; this health or survivor bias could have reduced the strength of the induced abortion-breast cancer link, as we explain above. The authors note that a health or survivor bias may have affected their data, because women with induced or spontaneous abortions at a young age who have breast cancer may tend to have a "poor prognosis (16), it could be that those women with breast cancer whom we were unable to interview because of serious illness or death may have been more likely to have had an induced abortion than the women we did interview. If this bias were present, we would have underestimated the risk of breast cancer that is associated with induced abortion."¹³²
- **Reporting difficulty around abortion law change.** Some of the reproductive years of some fraction of the women studied would have taken place prior to abortion's 1970 legalization in Washington State,¹³³ but as the authors note, the study is comprised of "women in whom most or all of their reproductive years occurred after 1970," and most of the abortions included took place following its legalization.

In addition to containing a large sample, the study's strength is that its "primary focus...was on the difference in the subsequent risk of breast cancer between pregnant women who did and did not choose to terminate that pregnancy but who, based on their demographic characteristics and child-bearing histories, were otherwise at similar risk." Hence, in analyzing the risk of induced abortion, the authors control for a variety of other factors, such as age, family history of breast cancer, and age at first birth. (Daling et al. even

¹³¹ 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.

¹³² *Id.* at 1589.

¹³³ National Abortion Federation, "History of Abortion"; http://www.prochoice.org/about_abortion/history_abortion.html (accessed April 19, 2013).

control for religion in their analyses for induced abortion and so attempt to control for any effect of “reporting bias” on the part of devout women.)

- **Induced abortion.** The authors found that induced abortion contributed to breast cancer risk. Having any abortion history contributed to one’s risk of breast cancer, relative to having no induced abortion history. Within this category, having one induced abortion had a positive, significant influence on breast cancer risk and having two or more induced abortions had a marginally significant, positive influence on breast cancer risk.
- **Age at first induced abortion.** First induced abortions before age 18 and first induced abortions at or after age 30 were both associated with a marked, significant increase in breast cancer risk. The effects of first induced abortions between ages 18 and 19 and between ages 20 and 29 were marginally significant and positive.
- **Gestational period at induced abortion.** Induced abortions between nine and 12 weeks’ gestation had a significant, positive influence on breast cancer risk. Induced abortions at or before eight weeks’ gestation had a marginally significant and positive influence on breast cancer risk, and induced abortions at or after 13 weeks’ gestation were not found to have any significant influence.
- **Age at first induced abortion and gestational period at induced abortion.** Further analyses showed that first induced abortions among girls younger than 18 between nine and 24 weeks’ gestation (though not before eight weeks’ gestation) had a large, positive, significant influence on breast cancer risk, relative to completed first pregnancies.

Relative to completed first pregnancies, first induced abortions in women aged 30 or older before eight weeks’ gestation and between nine and 24 weeks’ gestation had a positive, significant influence on breast cancer risk. It is to be noted that these analyses were conducted with very small subsamples of women.

No significant association was found between week of gestation at induced abortion, age at first induced abortion, and breast cancer risk among women aged 18 to 19 or aged 20 to 29 at their first induced abortion.

- **Induced abortions relative to timing of first full-term pregnancy.** Both induced abortions before and after a first birth were found to have a marginally significant, positive influence on breast cancer risk, relative to women who had been pregnant but had never had induced abortions. However, induced abortions in nulliparous women (i.e., women who *never* gave birth) were found to have a positive, significant influence on breast cancer risk relative to women who had been pregnant but had never had induced abortions.
- **Induced abortions relative to timing of first lactation.** Induced abortions taking place after a woman first lactated had a positive, significant influence on risk of breast cancer, relative to parous women who had lactated but never aborted. An induced abortion more than 10 years before lactating had a

positive, significant influence on breast cancer risk, relative to parous women who never aborted. The influence of induced abortion five or fewer years, or six to 10 years, before lactating was not found to be significant. No significant differences were found regarding the timing of their induced abortions (i.e., “before first birth,” “not until after first birth”) between parous women who never lactated.

- **Duration between first induced abortion and diagnosis of breast cancer (and comparable date for controls).** The category representing 10 to 14 years between first induced abortion and date at diagnosis was positive and significant. The category representing an interval of zero to nine years was positive and marginally significant, and the category representing 15 or more years was not significant. This is in line with the hypothesis that detectable breast cancer takes eight to 10 years to develop.
- **Stage of development.** Induced abortion was also found to have a positive, significant influence on breast cancer diagnosed at the *in situ* or local stages and at the regional or distant stages.
- **Induced abortion and family history of breast cancer.** Induced abortion among women with no family history of breast cancer had a marginally significant and positive influence on breast cancer risk. However, among women whose sister, mother, aunt, or grandmother had breast cancer, induced abortion had a positive, significant influence on breast cancer risk. This was particularly true in the case of first abortions before age 18 and at or after age 30.
- **Spontaneous abortion.** No significant association was found between breast cancer risk and history of spontaneous abortion, number of spontaneous abortions, age at first spontaneous abortion, timing of first spontaneous abortion (i.e., before or after first birth), or duration between first spontaneous abortion and diagnosis with breast cancer (and comparable date for controls). However, relative to women who had ever given birth and had never had a spontaneous abortion, a spontaneous abortion at or before eight weeks’ gestation had a marginally protective influence on breast cancer risk.

h) 1995 Lipworth study

A study of abortion in Greece¹³⁴ found induced abortion to have a positive, significant influence on breast cancer risk. The study is marked by health or survivor bias and failure to distinguish between first- and second-trimester spontaneous abortions, but it has the benefit of being conducted in a clinical environment, which would discourage underreporting.

The Lipworth study contained 820 cases diagnosed with breast cancer between January 1989 and December 1991 in hospitals around Athens. The study also included

¹³⁴ Loren Lipworth, Klea Katsouyanni, Anders Ekblom, Karin B. Michels, and Dimitrios Trichopoulos, “Abortion and the Risk of Breast Cancer: A Case-Control Study in Greece,” *International Journal of Cancer* 61 (1995): 181-184.

two matched control groups, comprised of 795 female orthopedic patients and 753 hospital visitors.

- **Health or survivor bias, differences between cases and controls not demonstrated.** Women with a previous history of breast cancer were excluded as controls; this health or survivor bias could have skewed the study's results away from induced-abortion breast cancer linkage. Additionally, the authors did not identify differences between cases and controls in their study. They should have done so in order to demonstrate that cases and controls were alike across other potential breast cancer risk factors.¹³⁵
- **Pregnancy outcomes.** Induced abortion was found to have a positive, significant influence on breast cancer risk, as was "spontaneous and/or induced abortion." A general analysis of induced and spontaneous abortion "adjusted for age, parity status, age at first birth, menopausal status, Quetelet's index [i.e., body mass index] and alcohol intake" showed no significant association between spontaneous abortion and breast cancer risk. (Similar controls were applied to odds ratios produced by regressions elsewhere in the study, though some controlled for age at first birth instead of parity status.)
- **Too-simple analysis of induced abortion.** The authors did not assess the effect of gestational stage at the time of abortion or of repeated abortions.
- **Pregnancy outcomes and parity status.** When broken down by parity, no significant effect was found for any type of abortion in nulliparous women. No significant difference was found between parous aborting women and nulliparous women with no abortion history. Relative to parous women with no abortion history, parous women with a history of induced abortion were found to be at increased risk of breast cancer. A history of both induced and spontaneous abortion was also found to have a positive, significant influence on breast cancer risk. No significant influence was found for spontaneous abortion. Additional adjustments for number of full-term pregnancies, total number of pregnancies, "energy intake," and fruit and vegetable consumption did little to shift these odds ratios.
- **No distinction between first- and second-trimester spontaneous abortions.** Lipworth et al. do not distinguish between first- and second-trimester spontaneous abortions.
- **Pregnancy outcomes relative to timing of first full-term pregnancy.** Lipworth et al. further broke down abortions by distinguishing them by their timing relative to first full-term pregnancy. No significant difference was found between parous aborting women and nulliparous women with no abortion history. However, relative to parous women with no abortion history, both induced abortion before first full-term pregnancy and induced abortion after

¹³⁵ Other potential breast cancer risk factors could be confounded with factors of interest, such as induced abortion.

first full-term pregnancy had a positive, significant influence on breast cancer risk. No significant effect was detected for spontaneous abortion. Again, adjustments for “energy intake,” fruit and vegetable consumption, and alcohol consumption did little to shift these odds ratios.

The authors also note that when their analysis of abortion relative to first full-term pregnancy was confined to women under 35, the risk of induced abortion was heightened for women aborting before first full-term pregnancy compared to nulliparous women with no abortion history, though “the estimate...is unstable.”

The authors caution readers (as other authors do) to regard their findings with some reserve, due to the possibility that “information bias” could be responsible for the connection in their study between induced abortion and breast cancer risk, because “the attribution of more than 50 [percent] of spontaneous abortions to chromosomal abnormalities that are unlikely to affect the associated hormonal status during the pregnancy should have placed spontaneous abortions as a group in an intermediate position between those with no abortion of any type and those with induced abortion.” However, if recall bias actually affects studies to the degree that many authors argue it does, the Lipworth study is all the more useful. As the authors also note, “Information bias with respect to induced abortion is certainly possible but not likely to be large in this study, given the permissive social environment with respect to induced abortion in Greece and the fact that the interviews were conducted in the hospital setting by hospital-associated health professionals.”

i) 1995 Bu study (abstract)

A study of women in Harbin, China,¹³⁶ found a statistically significantly increased risk of breast cancer among women 45 and younger who had had one induced abortion or two or more induced abortions. This increase in risk was greater when the analysis was confined to women younger than 35. The brief abstract makes no mention of the inclusion of several breast cancer risk factors in its model, its results are generalizable only to parous women, and the mode of its relatively simple analysis of a fairly small sample is unclear, but the study’s confinement to young women could diminish the effects of any health or survivor bias introduced by its “rearward-looking” analysis.

- **Small sample, limited generalizability.** The study was confined to parous women younger than 45 at the time of their diagnosis with breast cancer. Its confinement to parous women limits its generalizability. The 232 cases were diagnosed between October 1990 and December 1992. Each case was matched for age and neighborhood with two controls. Their sample is thus relatively small. Information was obtained regarding the reproductive history of cases and controls.

¹³⁶ L. Bu, L.F. Voigt, Z. Yu, K.E. Malone, and J.R. Daling, “Risk of breast cancer associated with induced abortion in a population at low risk of breast cancer,” *American Journal of Epidemiology* 141 (1995): S85 (abstract 337).

- **Potential omitted variable bias, unclear means of analysis, an attempted reduction of health or survivor bias.** This abstract makes no mention of many other breast cancer risk factors, and its mode of analysis is unclear. Though many studies assessing the histories of breast cancer patients and controls risk introducing health or survivor bias into their analysis, this study reduces that risk by confining itself to women under age 45. These women are still within their reproductive years, and the risk of women being diagnosed with breast cancer “too early” and selecting out of the cohort is therefore reduced.
- **Induced abortion.** Bu et al. found a history of one or two or more induced abortions to have a positive and significant influence on breast cancer risk. The abstract makes no mention of a temporal assessment of induced abortions and live births, or of maternal age or gestational period at induced abortion. The authors found the influence of induced abortion to be stronger when they restricted their analysis to women under 35 at the time of their diagnosis.

j) 1995 Andrieu multiple re-analysis

Researcher Andrieu and colleagues analyzed studies conducted in France, Australia, and Russia in order to examine potential interaction between family history of breast cancer, abortion history, and risk of breast cancer.¹³⁷ The study’s analysis found one induced abortion to have a positive, significant influence on breast cancer risk. The design of some studies and the data the re-analysis chose to include or exclude from the studies could have introduced error and bias into their analyses; Andrieu et al. do not distinguish between first- and second-trimester spontaneous abortions; the authors neglect to assess maternal age and gestational stage at induced abortion; and in assessing the effect of abortion timing, they fail to distinguish between induced and spontaneous abortion.

- **Health or survivor bias, unsuitable data collection means and handling.** Individual odds ratios from each study were adjusted for various potential confounding factors, and a combined odds ratio was produced in each analysis from the available data from all studies. However, the design of some of these studies could introduce biases that could skew the effect of induced abortion. The 1988 Rohan study was based on in-home interviews, and its analyses were restricted to cases with first diagnoses of breast cancer. Cases in the 1988 Luporsi study were confined to those with “infiltrating” (that is, invasive) breast cancer, and women with a history of breast cancer were excluded as controls. Malignant controls included in the 1991 Clavel study were actually excluded from the Andrieu multiple re-analysis.

¹³⁷ N. Andrieu, S.W. Duffy, T.E. Rohan, M.G. Lê, E. Luporsi, M. Gerber, R. Renaud, D.G. Zaridze, Y. Lifanova, and N.E. Day, “Familial Risk, Abortion and Their Interactive Effect on the Risk of Breast Cancer—A Combined Analysis of Six Case-Control Studies,” *British Journal of Cancer* 72, no. 3 (1995): 744-751.

- **Incomplete pregnancy.** The re-analysis found no significant associations in an analysis of general abortion (a combined category of induced and spontaneous abortions) and breast cancer risk, other than a marginally significant negative influence with two or more abortions in the unpublished Zaridze data.
- **Induced abortion.** When induced and spontaneous abortion were distinguished, data from the 1988 Rohan study and the results of the combined data of five studies both showed one induced abortion to have a significant, positive influence on breast cancer risk. The 1988 Luporsi study showed one induced abortion to have a marginally significant positive influence on breast cancer risk.

The 1984 Lê study found two or more induced abortions to have a marginally significant positive influence on breast cancer risk, and the unpublished Zaridze data showed two or more induced abortions to have a marginally significant *negative* (i.e., protective) influence on breast cancer risk.

- **Too-simple analysis of induced abortion.** Andrieu et al. do not assess induced abortion with regard to maternal age or gestational stage.
- **Spontaneous abortion.** No significant association was found in any study for any number of spontaneous abortions.
- **No distinction between first and second-trimester spontaneous abortions.** Note that Andrieu et al. do not distinguish between first- and second-trimester spontaneous abortions.
- **Incomplete pregnancy regarding timing of first full-term pregnancy.** When general abortions were broken down by timing relative to first full-term pregnancy, no significant effect was distinguished in any of the six studies examined or in the combined analysis of the data.
- **Inconsistent distinction between induced and spontaneous abortion.** Andrieu et al. do not distinguish induced from spontaneous abortion when they perform their analyses of abortions with respect to the timing of first full-term pregnancy.
- **Family history of breast cancer.** In all studies but the 1988 Rohan study (in which a marginally significant positive association was detected), as well as in the analysis of all data combined, a positive, significant association was detected between family history of breast cancer and breast cancer risk.

3. Full, modern epidemiological studies

k) 1999 Fioretti study

An Italian study¹³⁸ comprised of data from the 1987 and 1995 La Vecchia studies showed a risk of breast cancer among nulliparous women having abortions late in their reproductive lives. The study is of limited generalizability due to its restriction to nulliparous women, is marked by health bias, does not distinguish between first- and

¹³⁸ F. Fioretti, A. Tavani, C. Bosetti, C. La Vecchia, E. Negri, F. Barbone, R. Talamini, and S. Franceschi, "Risk factors for breast cancer in nulliparous women," *British Journal of Cancer* 78, no. 11/12 (1999): 1923-1928.

second-trimester spontaneous abortions, does not apply multiple controls uniformly across its analyses, and in its more sophisticated analyses (e.g., age at first abortion) fails to distinguish between induced and spontaneous abortions.

Fioretti et al. conducted a study deliberately designed to evaluate breast cancer risk among nulliparous women, whom they acknowledge are at increased risk of breast cancer. The study was comprised of 1,041 nulliparous cases between the ages of 22 and 79 and 1,002 nulliparous controls aged 15 to 79 living in six different geographic areas in Italy.

- **Limited generalizability.** Fioretti et al. write that the study's restriction "to nulliparae avoids the possible modifying effect or confounding from full-term pregnancy, and allows a more precise assessment of the role of other hormonal risk factors for breast cancer." This would limit the study's generalizability to nulliparous women. Women were "not included [as controls] if they had been admitted for gynaecological, hormonal or neoplastic diseases," and this exclusion could introduce health bias into the analyses.
- **Lack of (consistently applied) multiple controls.** Note that Fioretti et al. do not apply multiple controls uniformly across their analyses. Lacking multiple controls, this study may incorrectly attribute to one variable the influence of *other* variables on breast cancer.
- **Pregnancy outcomes.** No significant association was detected between breast cancer and spontaneous abortions, induced abortions, or total number of abortions (combined category for spontaneous and induced).
- **Age at first incomplete pregnancy.** Using women experiencing a first abortion (combined category for spontaneous and induced) prior to age 30 as a reference category, experiencing a first abortion at or after age 30 had a positive, significant influence on breast cancer risk within the general sample and among postmenopausal women. No significant association was detected between breast cancer and age at first abortion among premenopausal women.
- **Inconsistent distinction between induced and spontaneous abortion, too-simple analysis of induced abortion, lack of distinction between first- and second-trimester spontaneous abortions.** That this study assesses spontaneous and induced abortions only in a combined category when examining the influence of age at first abortion and number of abortions is a shortcoming. The authors also did not distinguish abortions based on the gestational stage at which they occurred. Note that Fioretti et al. do not distinguish between first- and second-trimester spontaneous abortions.
- **Age at menarche.** Within the general sample and among postmenopausal women, no significant association was detected between age at menarche and breast cancer risk. However, among premenopausal subjects, menarche at age 15 or later had a significant and negative (i.e., protective) influence on breast cancer risk relative to menarche younger than age 12. As a trend, each

year's delay of menarche was associated with a significant decrease in breast cancer risk.

- **Age at menopause.** Among postmenopausal women, commencing menopause between the ages of 45 and 49, between the ages of 50 and 52, and commencing menopause at age 53 or later was associated with a significantly increased risk of breast cancer, relative to commencing menopause before age 45. As a trend, increasing age at menopause had a positive, significant influence on breast cancer risk. No significant effect was detected for experiencing artificial menopause.¹³⁹
- **Length of menstrual periods.** No significant association was detected between breast cancer and duration of menstrual periods.
- **Oral contraceptive use.** Ever using oral contraception, or oral contraceptive use for two years, had a positive, significant influence on breast cancer risk, relative to never using oral contraceptives.
- **“Hormone replacement therapy” use.** Relative to never using hormone replacement therapy, no significant effect was detected for “hormone replacement therapy” use. No significant effect was detected with two or more years’ use of “hormone replacement therapy.”
- **Family history of breast cancer.** First-degree family history of breast cancer was associated with an increased risk of breast cancer within the general sample and among both the pre- and postmenopausal subgroups.
- **History of benign breast disease.** A personal history of benign breast disease had a positive, significant influence on breast cancer risk within the general sample, among premenopausal women, and among postmenopausal women.
- **Educational attainment.** Relative to having seven or fewer years of education, having seven to 11 years of education and having 12 or more years of education had a positive, significant influence on breast cancer risk within the general sample and among premenopausal women. Among postmenopausal women, having seven to 11 years’ education had a positive, marginally significant influence on breast cancer, and having 12 or more years’ education had no significant influence. Relative to never being married, having ever been married had a positive, significant influence on breast cancer risk within the general sample, but it had no significant effect in either the premenopausal or postmenopausal subgroup.
- **Various risk factors.** No significant association was detected between breast cancer and body mass index, physical activity, or alcohol consumption in the general sample or in either subsample. As a trend, increased consumption of beta carotene (“a nonspecific indicator of fruit and vegetables” intake) was associated with a decreased risk of breast cancer among women in the general

¹³⁹ Artificial menopause involves the surgical removal of the ovaries. Women who undergo this procedure are often offered hormone replacement therapy.

sample and women in the postmenopausal subcategory. Among women in the general sample and postmenopausal women, those women who consumed 1,511.3 to 1,953 (kilo) calories daily were at an increased risk of breast cancer, relative to those who consumed fewer than 1,511.3 calories per day. No effect was detected for consuming more than 1,953 calories per day among women in the general sample or postmenopausal women, and no significant association was detected between breast cancer risk and number of calories consumed daily among premenopausal women.

The authors note that because “[m]ost estimates were consistent with available knowledge of breast cancer epidemiology...it is unlikely that parity is a major modifying factor of breast carcinogenesis.” Nulliparity is one of the most important risk factors in contracting breast cancer. Fioretti et al. are not contradicting this; they are saying parity may act *independent* of the other risk factors. While an interesting hypothesis, the authors would do well to prove this epidemiologically.

l) 2003 NCI workshop

By the year 2000, many studies had shown induced abortion to have a positive, statistically significant influence on breast cancer risk. The NCI website, which reported that the data were “inconclusive” and “inconsistent” from 1994 to 2002, changed its language in 2002: “The current body of scientific evidence suggests that women who have had either induced or spontaneous abortions have the same risk as other women for developing breast cancer.” The new web page also made no mention of the 1994 Daling study.

These alterations drew a reaction from some members of the U.S. Congress, which has budgetary and political oversight of the NCI. That year, 28 congressmen signed a letter asking the NCI to amend its website concerning the link between breast cancer and induced abortion, as a large quantity of the data demonstrated a risk.

The letter resulted in the removal of this page from the website, pending a February 2003 workshop on “Early Reproductive Events and Breast Cancer Risk” conducted by the NCI. One hundred scientists and breast cancer advocates participated in this three-day workshop; save for one dissenter—Joel Brind—they concluded that induced abortion was not a risk and did not merit further study. The workshop did note, however, that premature delivery was considered an “epidemiologic gap” requiring more study.¹⁴⁰

m) 2003 Becher study

A 2003 study¹⁴¹ in Germany designed to assess the importance of reproductive breast cancer risk factors among women genetically susceptible to breast cancer (the

¹⁴⁰ National Institutes of Health, National Cancer Institute, “Summary Report: Early Reproductive Events and Breast Cancer Workshop,” National Cancer Institute <http://www.cancer.gov/cancertopics/causes/ere/workshop-report/> (accessed January 3, 2013).

¹⁴¹ H. Becher, S. Schmidt, and J. Chang-Claude, “Reproductive factors and familial predisposition for breast cancer by age 50 years. A case-control-family study for assessing main effects and possible gene-environment interaction,” *International Journal of Epidemiology* 32 (2003): 38-50.

authors tested for a “gene-environment interaction”) found an increased risk of breast cancer with induced abortion. The Becher study, while marked (like many studies) by some degree of health or survivor bias, reporting no data on spontaneous abortion, and containing only a simple analysis of induced abortion (it does not, for example, examine the effects of repeated induced abortions), is uniquely beneficial to the field in that it is focused on women genetically predisposed to breast cancer.

The study included 706 cases diagnosed with *in situ* or invasive breast cancer in 40 hospitals in two regions in Baden-Württemberg, Germany. The women were mainly premenopausal and age 50 or younger at the time of their diagnosis between January 1992 and December 1995. The study also included two sets of controls: 252 sisters of cases and 1,381 age- and region-matched population controls identified through German population registries.

All women studied completed a survey requesting information on a variety of potential breast cancer risks: “demographic and anthropomorphic factors, menstrual, reproductive and breast feeding history, use of contraceptives and exogenous hormones, medical and screening history, family history of cancer, selected occupational exposures, diet, smoking history, and alcohol consumption.” Detailed information was also obtained about breast cancer across four generations. The authors delineate some of the differences between their cases and both groups of controls.

To detect genetic susceptibility to breast cancer, the authors relied on family history of ovarian and breast cancer. Using this information, Becher et al. estimated the likelihood that a study participant was at an increased risk of breast cancer due to a genetic susceptibility to the disease.

- **Health or survivor bias.** Selection out of the survey, and the resultant introduction of health bias, is a problem with this study. Women having suffered from breast cancer, found for the “control” population, were excluded. Thus, there are more women in the control group who have experienced abortions but must not have experienced breast cancer. Though a relationship between induced abortion and breast cancer is detected, the study’s very design may have biased the strength of that relationship to be too weak.
- **Induced abortion.** Multivariate regressions showed that ever having an induced abortion had a positive and significant influence on breast cancer risk both within the general sample and among only parous women. No significant association was detected between induced abortion and breast cancer when the analysis was restricted to the cases and their sister controls.
- **Unsophisticated analysis of induced abortion.** No distinction was made based on timing of abortion relative to first full-term pregnancy (if any); though the effect of induced abortion is controlled for parity, this does not consider whether or not a woman had the protection of full-term pregnancy *at the time of her induced abortion*. The analysis also does not assess the influence of the

age of the mother at the time of her abortion, the gestational period in which the abortion took place, or the influence of repeated induced abortions.

- **No reported data on spontaneous abortion.** Becher et al. do not note any findings on spontaneous abortion.
- **Induced abortion and genetic vulnerability to breast cancer.** Induced abortion was not found to influence breast cancer rates differently for women with genetic susceptibility to breast cancer and women without that susceptibility.
- **Number of full-term pregnancies and parity status.** Becher et al. found that, within their general sample, no significant effect on breast cancer risk was detected with number of full-term pregnancies or with parity as a binary variable (relative to nulliparity).

Among only parous women, having three or more full-term pregnancies had a negative (i.e., protective) and significant influence on breast cancer risk, relative to having only one full-term pregnancy. The authors note in text that “[t]here was a statistically significant decrease in risk with increasing number of full-term pregnancies among parous women.” In the analysis of only the cases alongside their sister controls, no significant effect on breast cancer was detected for having one or three or more full-term pregnancies, but having two full-term pregnancies had a positive, significant influence on breast cancer risk, relative to nulliparity. Becher et al. state that this is evidence that the protection that an increased number of full-term pregnancies affords is lessened among women who are genetically susceptible to breast cancer. Indeed, when parity was analyzed in concert with genetic susceptibility to breast cancer, the authors found that parity offered less protection to women genetically susceptible to breast cancer than to those who were not.

- **Age at first birth.** The authors note in text that they “did not observe an effect of age at first birth on breast cancer risk,” though they also note that “age at first life [sic] birth is typically highly correlated with number of life [sic] births.” Becher et al. found a significant negative correlation between increasing age at first live birth and number of live births.
- **Duration of breastfeeding.** When the analysis was conducted across all women, across only parous women, and among only cases and their sister controls, multivariate regressions showed an increased duration of breastfeeding had a negative (i.e., protective) and significant influence on breast cancer risk. No significant interaction was found between breastfeeding, genetic susceptibility to breast cancer, and breast cancer risk, though Becher et al. note that “the comparison of results from population controls...and sister controls...suggests a stronger protective effect when comparing with sister controls.”
- **Age at menarche.** No significant association was detected within the general sample, among parous women, or among the cases and their sister controls between breast cancer and age at menarche in the multivariate regression.

- **Family history of and genetic susceptibility to breast cancer.** Having a first-degree relative with breast or ovarian cancer had a large, positive, and significant influence on breast cancer risk. Increasing probability of carrying a genetic susceptibility also had a positive and significant influence on breast cancer risk. This factor was analyzed in various statistical manners: as a trend, by categories representing increased likelihood of being a gene carrier, and as a dichotomous variable (i.e., “is not likely a gene carrier” versus “is likely a gene carrier”). In all cases, risk of being a gene carrier was associated with increased breast cancer risk. All these risks were adjusted for induced abortion, number of full-term pregnancies, duration of breastfeeding, and age at menarche. The “gene carrier probability” model employed by Becher et al. is substantiated by these analyses: In all formulations, a higher probability of carrying such a deleterious gene is significantly associated with higher odds of contracting breast cancer.

n) 2006 Tehranian presentation (abstract)

A 2006 Iranian study found a statistically significant increased risk of breast cancer with induced abortion and with spontaneous abortions after 12 weeks’ gestation.¹⁴² The brief abstract makes no mention of the inclusion of several breast cancer risk factors in its model, the mode of its relatively simple analysis of a fairly small sample is unclear, and it may be marked by health bias.

The study included 231 cases and 254 population controls and was conducted at a medical university in Mashhad in 2004. Cases and controls were matched “by age, menstruation, family history of breast cancer, breastfeeding, duration of oral contraceptive use, history of [“hormone replacement therapy,”] and body mass index.”

- **Small sample, neglect of potential breast cancer risk actors, unclear means of analysis.** Tehranian et al. do not make plain their mode of analysis and make no mention of controls for parity, number of full-term pregnancies, age at first full-term pregnancy, smoking, or alcohol consumption (though consideration of alcohol may be less crucial, given the fraction of the population that likely abstains from alcohol consumption due to religious beliefs).
- **Health or survivor bias.** It seems that women with breast cancer may have been excluded as controls, who are described as “general healthy population controls,” a health bias which could introduce error into their analyses and skew their results away from induced abortion-breast cancer linkage.

¹⁴² 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). Please note that only the abstract of this study is currently available.

- **Induced abortion.** Tehranian et al. report that women who had induced abortions prior to 12 weeks' gestation had a significantly larger breast cancer risk than women who had no induced abortion history.¹⁴³
- **Too-simple analysis of induced abortion.** The authors seem not to have assessed induced abortion relative to timing of first full-term pregnancy, maternal age at time of induced abortion, or number of induced abortions.
- **Spontaneous abortion.** Women who had one spontaneous abortion after 12 weeks' gestation had a significantly larger breast cancer risk than women with no history of spontaneous abortion. Women who had two or more spontaneous abortions after 12 weeks' gestation had a further (significant) increased risk of breast cancer, compared to women who had never had a spontaneous abortion. As noted earlier, these later spontaneous abortions (usually those that happen in the second trimester) differ from very early spontaneous abortions, which are usually due to hormone levels insufficient to maintain the pregnancy.

o) 2007 Naieni study

A 2007 study conducted in the province of Mazandaran in Iran showed a statistically significant increased risk of breast cancer with abortion.¹⁴⁴ This study may be skewed by health or survivor bias, conducts only an unsophisticated analysis of induced abortion, and does not distinguish between first- and second-trimester spontaneous abortions.

The Naieni study included 250 cases aged 22 to 80 chosen through the cancer registry of Babol Research Station, as well as 500 neighborhood-matched controls aged 19 to 77. The authors demonstrate the differences between their cases and controls. In addition to analyzing the effects of induced and spontaneous abortion, the authors implemented a wide variety of controls, such as first-degree family history of breast cancer, personal history of benign breast disease, oral contraceptive use, age at menarche, and menopausal status, as well as factors such as education and household income.

- **Health or survivor bias, and an attempted correction.** Though the Naieni study's rearward-looking analysis could introduce health or survivor bias, the authors interviewed relatives of deceased participants, a correction that could reduce the effect of this bias.
- **Induced abortion.** Induced abortion had a positive, precisely determinable influence on breast cancer risk.

¹⁴³ While some authors might attribute the size of the (substantial) effects conferred by induced abortion in the 2006 Tehranian study, by university education in the 2007 Naieni study, and by induced abortion in the 2011 Khachatryan study, to recall bias, we wonder whether the size of the effects is not a consequence of fewer carcinogenic channels in these societies. For example, Khachatryan et al. note that Armenians consume very little alcohol and that very few Armenian women have ever used "hormone replacement therapy" or oral contraception. This reduced exposure to carcinogens would statistically "clarify" any effect of induced abortion (or of any other relevant factor).

¹⁴⁴ Kourosh Holakouie Naieni, Ali Ardalan, Mahmood Mahmoodi, Abbas Motevalian, Yoosef Yahyapoor, and Bahareh Yazdizadeh, "Risk Factors of Breast Cancer in North of Iran: A Case-Control in Mazandaran Province," *Asian Pacific Journal of Cancer Prevention* 8 (2007): 395-398; http://www.apocp.org/cancer_download/Volume8_No3/395-398%20c_Naieni%204.pdf (accessed December 7, 2012).

- **Unsophisticated analysis of induced abortion.** The authors did not distinguish induced abortions based on their timing relative to first full-term pregnancy; though they control for parity, this does not assess the vulnerability status of the mother *at the time of her abortion*. They also do not distinguish based on age at first induced abortion, or gestational period at the time of the abortion.
- **Number of full-term pregnancies.** Relative to nulliparous women, women who had given birth to three, four, or five or more children had a marked, very precisely determinable reduction in breast cancer risk. With every child delivered, beginning with the third, one's breast cancer risk was significantly diminished. Increased number of full-term pregnancies, in general, was associated with a precisely determined reduction in risk of breast cancer.
- **Duration of breastfeeding.** Each month of breastfeeding was found to slightly (but precisely) reduce one's breast cancer risk.
- **Menopausal status.** Currently experiencing menopause was positively associated with breast cancer risk.
- **Family history of breast cancer.** First-degree family history of breast cancer was positively associated with breast cancer risk.
- **Educational attainment.** The authors found a large, positive, and significant association between college education and breast cancer.
- **Body mass index.** A small but positive and precisely determinable association was also found between body mass index (as a trend) and breast cancer.
- **Various risk factors.** No significant influence on breast cancer risk was found for spontaneous abortion (Naieni et al. do not distinguish between first- and second-trimester spontaneous abortions), age at first birth, age at menarche, history of benign breast disease, history or duration of oral contraceptive use, history of irregular menstruation, smoking history, or monthly family income.

p) 2009 Dolle study

A study in the U.S. by Jessica Dolle and colleagues¹⁴⁵ of risk factors for triple-negative breast cancer found evidence of an association between abortion and breast cancer.¹⁴⁶ The study is marked by health or survivor bias, failed to include a variable for spontaneous abortion in their analyses, and conducted only a simple analysis of induced abortion.

The Dolle study included 744 white patients aged 21 to 45 who were diagnosed with invasive breast cancer between January 1983 and April 1990 and identified through the Seattle-Puget Sound SEER cancer registry, as well as 542 patients aged 21 to 44 who were diagnosed with invasive breast cancer between May 1990 and December 1992

¹⁴⁵ Jessica M. Dolle, Janet R. Daling, Emily White, Louise A. Brinton, David R. Doody, Peggy L. Porter, and Kathleen E. Malone, "Risk Factors for Triple-Negative Breast Cancer in Women Under the Age of 45 Years," *Cancer Epidemiology, Biomarkers and Prevention* 18, no. 4 (2009): 1157-1166.

¹⁴⁶ Triple-negative breast cancer cases are those in which cells' estrogen receptors, progesterone receptors, and HER2 receptors are "negative." These cases of breast cancer are particularly difficult to treat.

and identified through the Seattle site of the Women's Interview Study of Health. To these two sets of cases were matched, respectively, a set of 961 controls and a set of 608 controls. Both sets of controls were identified by random digit dialing.

The authors included controls for age, family history of breast cancer, and lactation history among parous women, as well as controls for oral contraceptive use. For certain models, race, education, income, body mass index, smoking, alcohol consumption, age at menarche, number of live births, and age at first birth were also included as controls.

- **Health or survivor bias, and an attempted correction.** Though the Dolle study's rearward-looking analysis could introduce health or survivor bias into its analysis, the authors' restriction of the study to women yet in their reproductive years is a correction that could reduce the effect of this bias.

The Dolle study included only invasive cases of breast cancer and excluded *in situ* cancer, but it did so to facilitate a focus on invasive triple-negative breast cancer. Their exclusion of *in situ* cancer had a purpose, but it may have introduced survivor bias and weakened any effect of induced abortion on breast cancer risk.

- **Induced abortion.** In regressions analyzing risks for all types of breast cancer combined, ever having had an induced abortion had a positive, significant influence on breast cancer risk. Induced abortion history also had a positive and significant influence on non-triple-negative breast cancer risk (i.e., the category of breast cancers that excluded triple-negative breast cancer), but it had no significant influence on triple-negative breast cancer risk.
- **Unsophisticated analysis of induced abortion.** The authors did not parse out the risks associated with gestational period at induced abortion, maternal age at first induced abortion, or the timing of induced abortion relative to first full-term pregnancy. Dolle et al. also did not assess the effects of repeated induced abortions.
- **No reported data on spontaneous abortion.** The authors did not include a variable for miscarriage.
- **Age.** Being between the ages of 30 and 34, 35 and 39, and 40 and 45 had a positive and significant influence on general breast cancer risk, relative to being younger than 30. Being between the ages of 30 and 34 had a positive and marginally significant influence on non-triple-negative breast cancer risk, and being between 35 and 39 years or 40 and 45 years old had a positive and significant influence. Increasing age, as a trend, was found to be positively associated with general breast cancer risk and non-triple-negative breast cancer risk. No significant association was detected with any age category or with the trend of increasing age and triple-negative breast cancer risk.
- **Number of live births.** Having four or more live births had a negative (i.e., protective) and marginally significant influence on general breast cancer risk and non-triple-negative breast cancer risk, relative to having no live births.

As a trend, an increasing number of live births was associated with reduced breast cancer risk.

- **Age at first birth.** First giving birth prior to age 20 had a negative and marginally significant influence on general breast cancer risk and non-triple-negative breast cancer risk. As a trend, increasing age at first birth was precisely associated with increased general breast cancer risk, triple-negative breast cancer risk, and non-triple-negative breast cancer risk.
- **Age at menarche.** Experiencing menarche between the ages of 13 and 14 had a negative (i.e., protective) and marginally significant influence on general breast cancer risk and non-triple-negative breast cancer risk, relative to experiencing menarche between the ages of eight and 12. Experiencing menarche at or after age 15 had a negative (i.e., protective) and marginally significant influence on triple-negative breast cancer risk, relative to experiencing menarche between the ages of eight and 12. As a trend, older age at menarche was negatively associated with general breast cancer risk and triple-negative breast cancer risk.
- **Family history of breast cancer.** First-degree and second-degree family history of breast cancer had a positive and significant influence on general breast cancer risk, triple-negative breast cancer risk, and non-triple-negative breast cancer risk.
- **Oral contraceptive use.** Using oral contraception for at least one year had a positive, marginally significant influence on general breast cancer risk and a positive, significant influence on triple-negative breast cancer risk, relative to having used oral contraception for under one year (or never using oral contraception).
- **Duration of oral contraceptive use.** Using oral contraception for three to fewer than six years, or for six or more years, had a positive and marginally significant influence on general breast cancer risk and a positive and significant influence on triple-negative breast cancer risk, relative to having used oral contraception for under one year (or never using oral contraception). As a trend, duration of oral contraceptive use in years (among those who had used oral contraception for a year or more) was positively associated with triple-negative breast cancer risk.
- **Age at first oral contraceptive use.** Commencing oral contraceptive use prior to age 18 had a positive and significant influence on general breast cancer risk, triple-negative breast cancer risk, and non-triple-negative breast cancer risk, relative to having used oral contraception for under one year (or never using oral contraception). Commencing use between the ages of 18 and younger than 22 had a positive and significant influence on triple-negative breast cancer risk. Commencing use after age 22 had a positive and marginally significant influence on triple-negative breast cancer risk, relative to having used oral contraception for under one year (or never using oral contraception). As a

trend, earlier age at commencement of oral contraceptive use (among those who had used oral contraception for a year or more) was associated with increased general risk of breast cancer.

- **Time since first use of oral contraception.** A period of 15 to fewer than 20 years or 20 or more years since first use of oral contraception had a positive and marginally significant influence on general breast cancer risk, relative to never having used oral contraception or having used oral contraception for under one year. However, for all categories representing a period of time since first oral contraceptive use (one to fewer than 15 years, 15 years to fewer than 20 years, and 20 or more years), a positive and significant influence was detected for triple-negative breast cancer risk.
- **Time since last use of oral contraception.** Relative to having used oral contraception for under one year (or never using oral contraception), a period of one to fewer than five years since last use of oral contraception had a positive and significant influence on general breast cancer risk. A period of 10 to fewer than 15 years since last use of oral contraception had a positive and marginally significant influence on general breast cancer risk. However, no significant influence on general breast cancer risk was found for current use of contraception.

A positive and significant influence on non-triple-negative breast cancer was found for a period of one to fewer than five years since last use of oral contraception. However, for all categories save one representing a period of time since last oral contraceptive use (current oral contraceptive use, one to fewer than five years, five to fewer than 10 years, and 10 to fewer than 15 years, but *not* 15 or more years), a positive and significant influence was found for triple-negative breast cancer risk.

As a trend, an increasing number of years since last use of oral contraception was significantly associated with reduced risk of triple-negative breast cancer (among those who had used oral contraception for a year or more).

- **Other oral contraceptive use.** The authors conduct further analyses of the effects of oral contraceptive use based on various other factors, but a detailed analysis of the effects of oral contraception is outside the scope of this study.
- **Educational attainment.** Relative to not graduating from college, being a college graduate had a positive and marginally significant influence on general breast cancer risk and non-triple-negative breast cancer risk, but not on triple-negative breast cancer risk.
- **Various risk factors.** No association was found between breast cancer risk and race, income, body mass index, smoking, alcohol consumption, or lactation history.

q) 2009 Xing study

A study of breast cancer subtypes in China in 2009 found evidence that abortion was associated with an increased risk of breast cancer.¹⁴⁷ (For an explanation of the different subtypes of breast cancer, see Section II, B.) The study is marked by health or survivor bias, conducts only an unsophisticated analysis of induced abortion, and did not distinguish between first- and second-trimester spontaneous abortions.

The Xing study included a total sample of approximately 3,000, which was comprised of 1,417 breast cancer patients diagnosed at a hospital in Shenyang, China, between 2001 and 2009 and 1,587 controls identified in Shenyang City. Xing and colleagues developed a model controlling for many reproductive factors associated with (or thought to be associated with) different types of breast cancer, including parity status, age at menarche and first live birth, menopausal status, and first-degree family history of breast cancer.

- **Health or survivor bias.** Women with prior breast cancer diagnosis were excluded as controls, a health or survivor bias which could have skewed their results away from induced abortion-breast cancer linkage.
- **Pregnancy outcomes.** Induced abortion was found to positively and significantly influence risk of luminal A breast cancer. The authors suggest “that the high prevalence of luminal A breast cancer may not vary by race and ethnicity.”¹⁴⁸ Interestingly, one or more spontaneous abortions was found to significantly *reduce* risk of luminal A and luminal B breast cancer.
- **Unsophisticated analysis of induced abortion.** However, they did not distinguish the distinct risks associated with differently-timed abortions (gestational period at induced abortion, mother’s age at first induced abortion, or induced abortions relative to first full-term pregnancy, if any, though the authors did control for parity). Xing et al. also did not assess the effects of repeated induced abortions.
- **Lack of distinction between first- and second-trimester spontaneous abortions.** Note that Xing et al. do not distinguish between first- and second-trimester spontaneous abortions.
- **Parity.** Having one child significantly reduced the risk of luminal A, luminal B, and HER2-overexpressing breast cancer (the effects of having more than one child were not significant), relative to being nulliparous.
- **Breastfeeding.** Ever having breastfed significantly reduced the risk of luminal A, luminal B, HER2-overexpressing, and triple-negative breast cancer.
- **Age at menarche.** Experiencing menarche before age 13 significantly increased the risk of luminal A breast cancer.
- **Menopausal status.** Being postmenopausal significantly reduced one’s risk of luminal A and luminal B breast cancer.

¹⁴⁷ Peng Xing, Jiguang Li and Feng Jin, “A Case-Control Study of Reproductive Factors Associated with Subtypes of Breast Cancer in Northeast China,” *Medical Oncology* 27, no. 3 (2009): 926-931.

¹⁴⁸ *Id.* at 928.

- **Family history of breast cancer.** First-degree family history of breast cancer had a positive, significant influence on risk of luminal A breast cancer and a positive, marginally significant influence on risk of luminal B breast cancer.
- **Hysteromyoma.** History of hysteromyoma (a benign tumor in the uterus) had a negative (i.e., protective) and significant influence on risk of luminal A and HER2-overexpressing breast cancer.
- **Various risk factors.** No significant effects were found for age at first live birth or age at menopause.

r) 2009 Ozmen study

In 2009, a study in Turkey found induced abortion history contributed to a statistically significant increase in breast cancer risk.¹⁴⁹ The study is marked by health bias, conducts only an unsophisticated analysis of induced abortion, and does not distinguish between first- and second-trimester spontaneous abortions.

The Ozmen study was comprised of 1,492 breast cancer patients and 2,167 controls aged 18 to 70 visiting Istanbul University Medical Faculty hospital. (Some patients were also selected from the authors' breast cancer database.) The authors built a moderately thorough model and specified the differences between cases and controls. Alcohol consumption was consciously excluded from statistical analysis because of the very limited alcohol intake among Turkish women.

- **Health or survivor bias.** Women with hormonal diseases were excluded from the control group; this exclusion is a health bias that could have diminished the demonstrated effect of induced abortion on breast cancer risk.
- **Induced abortion.** Regressions with multiple controls showed induced abortion to have a positive, significant influence on breast cancer risk.
- **Unsophisticated analysis of induced abortion.** Ozmen et al. did not distinguish induced abortions based on the period of gestation at which they were performed or on their timing relative to first full-term pregnancy (if any), and they did not assess any possible effects of number of abortions or of maternal age at first abortion.
- **Lack of distinction between first- and second-trimester spontaneous abortions.** Note that Ozmen et al. do not distinguish between first- and second-trimester spontaneous abortions.
- **Various risk factors.** Age at or over 50 years had a significant, positive influence on breast cancer risk. Oral contraceptive use had a significant, negative influence on breast cancer risk. Other controls included body mass index, education, spontaneous abortions, smoking, breastfeeding and nulliparity.

¹⁴⁹ Vahit Ozmen, Beyza Ozcinar, Hasan Karanlik, Neslihan Cabioglu, Mustafa Tukenmez, Rian Disci, Tolga Ozmen, Abdullah Igci, Mahmut Muslumanoglu, Mustafa Kecer, and Atilla Soran, "Breast Cancer Risk Factors in Turkish Women— a University Hospital Based Nested Case Control Study," *World Journal of Surgical Oncology* 7, no. 37 (2009); <http://www.wjso.com/content/pdf/1477-7819-7-37.pdf> (accessed January 16, 2013).

s) 2011 Khachatryan study

In 2011, an Armenian study of the relationship between breast cancer and diabetes mellitus type two by Khachatryan and colleagues showed an increased risk of breast cancer with induced abortion.¹⁵⁰ The study is marked by health bias, was conducted over the telephone (which could generate underreporting), and conducts only a simple analysis of induced abortion with its small sample.

The Khachatryan study included 150 cases registered through the National Oncology Center and the Armenian-American Wellness Center between January 2002 and December 2008, as well as 152 controls with no prior history of breast diseases or (non-cosmetic) breast surgeries identified through random digit dialing. The sample was comprised of women aged 35 to 70, residing in Yerevan, Armenia, and participants were interviewed over the telephone.

The authors developed a model that controlled for many factors potentially related to breast cancer, including diabetes mellitus type two, age at menarche and at menopause, number of induced abortions and live births, age at first pregnancy, breastfeeding duration, family history of breast cancer, history of contraception and “hormone replacement therapy,” age, and body mass index. The authors noted the distribution of these factors among their cases and controls. Khachatryan et al. did not include a variable for alcohol consumption, and they did little analysis of the effects of “hormone replacement therapy” or oral contraceptives. As they note, alcohol consumption is relatively low in Armenia, and the percentage of Armenian women who have ever used oral contraceptives or “hormone replacement therapy” is in the low single digits.

- **Small sample, health or survivor bias, unsuitable data collection.** The sample assessed in the Khachatryan study is small; the implications of this are discussed above. Both the health bias introduced through the exclusion of controls with previous breast diseases or surgeries and the method of interview chosen (which may generate underreporting) could diminish any influence of induced abortion.
- **Induced abortion.** Multiple logistic regressions showed induced abortion to have a positive and significant influence on breast cancer risk.
- **Unsophisticated analysis of induced abortion.** The authors did not assess the differing effects of abortion based on its timing relative to first full-term pregnancy, if any (though their analysis did include a variable for parity), on gestational stage at the time of the abortion, or on age at first induced abortion.
- **Various risk factors.** Live birth had a negative (i.e., protective), significant influence on breast cancer risk. Increasing age at first pregnancy and diabetes mellitus type two had a positive, significant influence on breast cancer risk. No significant effect was found in multiple logistic regressions for breastfeed-

¹⁵⁰ L. Khachatryan, R. Scharpf, S. Kagan, “Influence of diabetes mellitus type 2 and prolonged estrogen exposure on risk of breast cancer among women in Armenia,” *Health Care for Women International* 32, no. 11 (2011): 953-971.

ing duration, age at menarche, age at menopause, age, body mass index, or “hormone replacement therapy.”

t) 2012 Jiang study

A 2012 Chinese study of abortion and breast cancer risk¹⁵¹ found an increased risk associated with a history of induced abortion. Having two induced abortions or three or more induced abortions contributed to increased breast cancer risk, and an increasing number of induced abortions was associated with increased breast cancer risk. Premenopausal women and postmenopausal women seemed to be affected differently by induced abortion. The authors fail to demonstrate the differences between their cases and controls; their study may be marked by health or survivor bias; they do not assess the effect of induced abortion with regard to timing of first full-term pregnancy, maternal age, or gestational period; they do not show the influence of several breast cancer risk factors; and they fail to distinguish between first- and second-trimester spontaneous abortions.

The Jiang study included 669 cases identified at Jiangsu Province Cancer Hospital from visits between June 2004 and December 2007 and through cancer registries in Huian, Jintan, Wuxi, and Taixing, all in Jiangsu Province, China. Six hundred eighty-two controls were randomly identified in towns near Taixing, Wuxi, Jintan, and Huian.

- **No demonstration of differences between cases and controls, neglect of some potential breast cancer risk factors.** The authors do not demonstrate the differences between their cases and controls, in tables or in text, except for those related to abortions. Jiang et al. show the crude risks associated with induced and spontaneous abortions (the general risks and risk broken down among pre- and postmenopausal women) and the risks adjusted for “age, marital status, educational level, occupations, body mass index, income/month, age at menarche, age at first birth, number of full-term pregnancies and non[-] full-term pregnancies.” They neglected other breast cancer risk factors, such as oral contraceptive use.
- **Health or survivor bias.** The study’s rearward-looking analysis may have introduced health or survivor bias into its analysis, which would weaken any effect of induced abortion.
- **Induced abortion.** The authors found that ever having an induced abortion contributed to breast cancer risk, even after the above-noted adjustments. Relative to having no abortions, the effects of one abortion were not significant after adjusting for the above factors, but having two or three or more induced abortions had a positive and significant

¹⁵¹ 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): 33-35; http://www.apjcpcontrol.org/page/popup_paper_file_view.php?pno=MzMtMzUgMTluMiZrY29kZT0yNzAxJmZubz0w&rpqubun=i (accessed December 7, 2012).

influence on breast cancer risk. As a trend, number of induced abortions was positively and significantly associated with breast cancer risk.

Induced abortion did not seem to affect premenopausal women in this sample as it did postmenopausal women. Among premenopausal women, induced abortion history had no significant effect on breast cancer risk; neither did having one or two abortions (relative to having no abortions). However, having three or more induced abortions was positively and significantly associated with breast cancer risk, even when adjusted for other factors. As a trend, number of induced abortions among premenopausal women was positively and modestly significantly associated with breast cancer risk.

Among postmenopausal women, ever having an induced abortion had a positive and significant influence on breast cancer risk, even when adjusted for the above-mentioned factors. Having one or two induced abortions had a positive and significant influence on breast cancer risk, but the effect of having three or more abortions was not significant after adjusting for other factors. As a trend, number of induced abortions among postmenopausal women was positively and very significantly associated with breast cancer risk.

- **Unsophisticated analysis of induced abortion.** Jiang et al. do not assess the influence of induced abortion relative to the timing of a first full-term pregnancy, though they do control for parity. Neither do they assess the effect of age at induced abortion or gestational period at induced abortion.
- **Spontaneous abortion.** The effects of spontaneous abortion in this sample were far less clear. Across the total sample, neither history of spontaneous abortion nor number of spontaneous abortions was found to have any significant effect on breast cancer risk. The same was true among premenopausal women.

Among postmenopausal women, the adjusted risk of ever having a spontaneous abortion was positive and significant, but no significant effect was found when number of spontaneous abortions was broken out.

- **Lack of distinction between first- and second-trimester spontaneous abortion.** Jiang et al. do not distinguish between first- and second-trimester spontaneous abortions.

u) 2013 Huang meta-analysis

A 2013 meta-analysis in China¹⁵² showed a statistically significant increased risk of breast cancer with abortion. This study references crude odds ratios rather than odds ratios adjusted for confounding breast cancer risk factors; a number of the articles referenced do not distinguish induced from spontaneous abortion; it does not assess abortions and live births temporally; and no significant effect for abortion is detected when the articles it deems of highest quality are assessed together. This meta-analysis references 36 articles from 14 provinces in China.

¹⁵² 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.

- **Health bias.** As we do not have access to the majority of the articles referenced in the meta-analysis, it is impossible for us to determine whether or not health bias affected these studies. However, the authors note that “no significant associations between [induced abortion] and breast cancer were found in cohort studies”¹⁵³ As we note earlier in our explanation of health bias, it may be that health bias is most pernicious in cohort studies, depending on how their populations are selected.

Huang et al. also found, in response to their inquiry as to “whether inadequate choice of referent group” could skew the results of their analysis, that a lower percentage of women with induced abortions in the control group was associated with a higher odds ratio for induced abortion. Clearly, careful randomization of the control population is essential. Additionally, this finding is rather in parallel with the point that if authors introduce health bias into their analyses by eliminating from their case and control population women with a previous history of breast cancer—and who, according to our theory, disproportionately have a history of induced abortion—and thereby shrink the disparity in the number of women with induced abortion history between cases and controls, they skew the odds ratio associated with induced abortion.

This finding—that a higher rate of induced abortion in the control population diminishes the overall study’s odds ratio—is crucial to note, particularly given the very high (over 50 percent) prevalence of induced abortion in the control groups of many studies (both cohort studies, both studies conducted in Shanghai, and a number of the studies ranked as being of highest quality) in the subgroups whose collective analyses detected no significant influence for induced abortion.

- **Induced abortion.** Huang et al. found that having a reproductive history involving at least one induced abortion had a positive, statistically significant influence on women’s breast cancer risk. This was the case in their analysis of studies that isolated induced abortion as well as in their analysis of studies that analyzed both induced and spontaneous abortion and in their analysis of all studies (those that did and those that did not distinguish induced from spontaneous abortion). Huang et al. did not conduct a temporal analysis of abortions and live births.
- **Number of induced abortions.** Huang et al. also found, when their investigation was further refined, that two or more induced abortions had a slightly larger (than one or more induced abortions) statistically significant influence on women’s breast cancer risk. This was the case in their analysis of studies that isolated induced abortion as well as in their analysis of studies that analyzed both induced and spontaneous abortion and in their analysis of all studies (those that did and those that did not distinguish induced from spontaneous abortion).

¹⁵³ *Id.* at 6.

Huang et al. found no significant influence on breast cancer risk with three or more induced abortions in studies of only induced abortion. In studies that assessed induced and spontaneous abortions, and in their overall analysis of both types of studies, having three or more induced abortions had a positive and significant influence on women's breast cancer risk. The authors note that, whereas in the United States "abortion is used predominantly to postpone first childbirth ... almost all [induced abortions] in China were performed to limit family size after the first child. Therefore, more [induced abortions] may imply an early age of childbirth. The protective effects of early childbirth will probably dilute the harmful effect of more [induced abortions]."

The authors also noted a possible bias toward underreporting of abortions, particularly among women who have procured more than two. They state that "this underestimation will inevitably create spurious associations between [induced abortion] and breast cancer, especially for more induced abortions."

- **Induced abortion and quality of articles reviewed.** The authors note that they ranked the articles in their meta-analysis by quality.¹⁵⁴ Eight studies received an "A" ranking (a score of 8 or 9 on their quality scale), 24 studies received a "B" ranking (a score of 5 to 7), and two received a "C" ranking (a score of 4 or lower). When the "A"-ranked studies were analyzed together, Huang et al. detected no significant influence for induced abortion. A positive, significant influence on breast cancer was detected for induced abortion in the analysis of the "B"-ranked studies and the "C"-ranked studies.
- **Induced abortion and other characteristics of studies reviewed.** No significant influence was found for induced abortion when the cohort studies were analyzed as a group, but the collective analysis of the case-control studies found induced abortion to have a positive, significant influence on breast cancer risk.

Joint analysis of the studies conducted in Shanghai found no significant influence for induced abortion on breast cancer risk. Collective analysis of the studies conducted in Jiangsu and of "other" regions of China found induced abortion to have a positive, significant influence on breast cancer.

Collective analysis of both hospital-conducted and population-conducted studies found induced abortion to have a positive, significant influence on breast cancer risk. The collective analysis of hospital-based studies found a larger effect for induced abortion than did the analysis of population-based studies.

¹⁵⁴ "The methodological quality of included studies was independently assessed by two reviews according to Newcastle-Ottawa Scale (NOS) based on three broad perspectives ... (1) the selection of the study groups; (2) the comparability of the groups; and (3) the ascertainment of exposure or outcome of interest, with scores ranging from 0 to 9." See 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): 3.

A positive, significant influence was detected for induced abortion on breast cancer risk in collective analyses of both studies with fewer than 800 participants and studies with 800 or more participants.

Likewise, induced abortion was found to have a positive, significant influence on women's breast cancer risk in collective analyses of both studies conducted before 2007 and studies conducted in or after 2007.

- **Omitted variable bias.** The Huang meta-analysis used crude odds ratios in its analyses rather than odds ratios adjusted for other factors that affect a woman's breast cancer risk (e.g., age at first birth, parity). They state that they did this because, among other reasons, not all the examined studies released adjusted odds ratios, and where studies did, the factors for which the crude odds ratios were adjusted differed.

Huang et al. add that the collective analysis of the 13 available adjusted odds ratios was close to their overall result based on the 36 crude odds ratios. They state that this "suggest[s] that the primary result was not substantially confounded by the un-adjusted factors."¹⁵⁵

- **Incomplete reporting and distinguishing between induced and spontaneous abortions.** It seems some of the articles included in this meta-analysis do not distinguish between induced and spontaneous abortion. However, Huang et al. perform both joint and separate analyses of studies that do and do not analyze induced abortion alone.

The authors note as justification for including studies that do not distinguish between induced and spontaneous abortion that spontaneous abortion likely occurs in 4.26 to 5.27 percent of Chinese women.¹⁵⁶ By contrast, in many of the studies in the meta-analysis, (unspecified type) abortion occurred in the control groups at a rate of over "50 [percent], suggesting that abortions tended to be primarily [induced abortion] rather than [spontaneous abortion]."¹⁵⁷

v) Summary

Though the independent influence of induced abortion may be smaller than the overall influence of long-term avoidance of full-term pregnancy (of which induced abortion, oral contraceptive use, and nulliparity or late age at first full-term pregnancy may be a part), our overview of the epidemiological research on induced abortion's influence on breast cancer risk shows the procedure to be an independent risk factor for the disease.

The reader will note that rarely do we report in the body of this document the numerical magnitude of any breast cancer risk increase conferred by induced abortion (or any other potential risk factor). The numerical risks associated with induced abortion

¹⁵⁵ 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): 8.

¹⁵⁶ *Id.* at 5.

¹⁵⁷ *Id.*

(and its related circumstances, which vary by study) are listed for each study in Appendix A. The reason behind this omission is simple: The quality of the studies assessing the relationship between induced abortion and breast cancer varies. The results produced by these studies are not easily comparable, and to weight the studies by strength and then compare their results would involve statistical work outside the scope of this review.

Furthermore, the societies in which these studies have been conducted are different. Any risk conferred by induced abortion will be clearer or more obscured based on other potential vulnerabilities and protections (e.g., cultural norms surrounding parity, early first full-term pregnancy) and potential carcinogenic exposures (that is, potential breast cancer risk factors, e.g., hormonal contraception, hormone replacement therapy, alcohol consumption) common to a society.

Regardless: Many studies concerning breast cancer risk have shown induced abortion to be a risk for breast cancer, in both western and non-western societies. Of the 72 epidemiological studies and three meta-analyses that differentiate induced from spontaneous abortions (or whose data have been re-analyzed to do so), 21 studies and two meta-analyses show some positive and significant relationship between induced abortion and breast cancer. Seven studies show a positive and marginally significant relationship between the two. Two ecological epidemiological studies have also shown an association between the two. (Again, for a listing of studies addressing the relationship between abortion and breast cancer, see Appendix A.)

Regarding their finding that first-trimester abortion before full-term pregnancy was positively associated with breast cancer, Pike et al. wrote in 1981, “If this finding is substantiated and if it continues to be a strong risk factor into middle age, it will be of major importance.”¹⁵⁸ Since Pike and colleagues wrote about the importance of this finding, it seems that other authors have treated similar findings—found in better-designed, stronger studies—with great caution.

Laing et al. in 1993 wrote that their results were merely tentative, due to potential reporting bias;¹⁵⁹ Daling et al. (1994) are fairly confident about their primary finding, that “induced abortion in the last month of the first trimester is associated with nearly a doubling of subsequent breast cancer risk,” but they term the very large increase they find in breast cancer risk among teenagers and over-30 women procuring abortions merely “hypotheses worthy of subsequent testing” because of the small samples assessed.¹⁶⁰ Lipworth et al. asserted in 1995 that, because of potential reporting bias (for which they do not test), “perhaps all that can be definitively stated is that any risk associated

¹⁵⁸ 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): 76.

¹⁵⁹ A.E. Laing, Florence M. Demenais, Rosemary Williams, Grace Kissling, Vivien W. Chen, and George Bonney, “Breast Cancer Risk Factors In African-American Women: The Howard University Tumor Registry Experience,” *Journal of the National Medical Association* 85 (1993): 938.

¹⁶⁰ 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): 1592.

with induced abortion is at most statistically marginal.”¹⁶¹ Naieni et al. (2007)¹⁶² and Xing et al. (2009)¹⁶³ scarcely address their findings regarding induced abortion in their respective discussions. Khachatryan et al. caution their readers regarding their findings on induced abortion in their 2011 study that “[r]eporting bias may further jeopardize this particular finding given the sensitive nature of induced abortions”;¹⁶⁴ though they state that more research is needed, they do not include induced abortion as a factor needing more research in their final set of research recommendations.¹⁶⁵

In short, the grains of salt with which we have been urged to take these studies’ findings are piling steadily higher. Of less concern is that these authors are treating their results with perhaps undue minimization. What is of great concern is that, despite the (at minimum) suggestive findings we have noted above, and despite some authors’ noting of the need for further investigation, the relevant medical authorities and institutions have not devoted more resources to further examination of the relationship between induced abortion and breast cancer.

E. Recall or Reporting Bias in Induced Abortion-Breast Cancer Studies

Theoretically, prospective studies (those that follow a cohort longitudinally prior to developing breast cancer) are the “gold standard” in reliability for establishing causation, but a study cannot be fairly called “gold standard” if data prospectively collected are not analyzed in a methodologically robust manner. As we have noted above, many of the most widely-cited prospective studies contained major biases and problems.

Retrospective studies (where a woman with already-developed breast cancer recalls her medical, birth, miscarriage, and induced abortion history) are considered by some to be much less reliable. The most commonly used argument against retrospective studies affirming the abortion-breast cancer link is the *suggestion* that recall bias, or reporting bias, has skewed the data toward linkage of induced abortion and breast cancer. This is the hypothesis that cases, who have all developed breast cancer, will be more likely to remember or admit that they have had induced abortions than controls, who are likelier to be healthy women and who will more likely hide their abortion histories. Such a difference in reporting would skew the data toward linkage between induced abortion and breast cancer.

¹⁶¹ Loren Lipworth, Klea Katsouyanni, Anders Ekblom, Karin B. Michels, and Dimitrios Trichopoulos, “Abortion and the Risk of Breast Cancer: A Case-Control Study in Greece,” *International Journal of Cancer* 61 (1995): 184.

¹⁶² Kouros Holakouie Naieni, Ali Ardalán, Mahmood Mahmoodi, Abbas Motevalian, Yoosef Yahyapoor, and Bahareh Yazdizadeh, “Risk Factors of Breast Cancer in North of Iran: A Case-Control in Mazandaran Province,” *Asian Pacific Journal of Cancer Prevention* 8 (2007): 398; http://www.apocp.org/cancer_download/Volume8_No3/395-398%20c_Naieni%204.pdf (accessed December 7, 2012).

¹⁶³ Peng Xing, Jiguang Li and Feng Jin, “A Case-Control Study of Reproductive Factors Associated with Subtypes of Breast Cancer in Northeast China,” *Medical Oncology* 27, no. 3 (2009): 928, 930.

¹⁶⁴ L. Khachatryan, R. Scharpf, S. Kagan, “Influence of diabetes mellitus type 2 and prolonged estrogen exposure on risk of breast cancer among women in Armenia,” *Health Care for Women International* 32, no. 11 (2011): 967.

¹⁶⁵ *Id.* at 968.

1. 1991 Lindefors Harris study

The most quoted study in support of recall bias, the 1991 Lindefors Harris¹⁶⁶ Swedish study, assesses data obtained through two studies, the 1986 Meirik study and the 1989 Lindefors Harris study. These two studies addressed the relationship between abortion and breast cancer in the same population using different study designs. The 1989 Lindefors Harris study linked records of induced abortions and breast cancer diagnoses, and the 1986 Meirik study 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. These disparities are the basis for their argument that women with breast cancer are more likely to disclose any induced abortion history. However, as we will explain below, their findings are an utterly insufficient basis for this conclusion.

- **Apparent disparities between cases and controls in underreporting.** The authors stated that over- and underreporting of abortions (i.e., more or fewer abortions reported in interviews than were noted in the national registries) were evident in their data. The authors noted that “there were induced abortions reported at interview for the years 1966-1974 from 26 breast cancer cases and 44 controls. The corresponding numbers from the register were 24 cases and 59 controls.” From this disparity they deduce that cases tend more to report their abortions than controls. If more sick women than healthy women report their abortions, they reason, then abortion will be perceived as being associated with breast cancer. In light of the gap between abortions reported in interviews and abortions listed in the registry they reference, Lindefors Harris et al. caution readers that relying on the interview-based study would have produced “an illusory 50 percent increase in breast cancer risk.”
- **Unsuitable data collection and comparison of unlike datasets.** However, there are problems with this assertion. Importantly, the interviews used in the 1986 Meirik study were conducted at home. The results of investigations on induced abortion conducted in the home will not be comparable to those conducted in a clinical environment, such as a hospital or doctor’s office. Findings generated from interviews conducted in participants’ homes will naturally be disposed to bias and underreporting, but this underreporting will not differ between cases and controls.
- **Assessing the charge of “overreporting.”** Furthermore, Lindefors Harris et al. consider the induced abortion registry as more reliable than women’s reports; as we will show below, this confidence is not necessarily justified. Again, the authors of the 1991 Lindefors Harris study note that 26 cases and 44 controls in their interviews claim to have had abortions and that there were 24 case abortions and 59 control abortions listed in the register. Whereas *fewer* control-procured abortions were found in the interviews than in the registry,

¹⁶⁶ 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.

more case-procured abortions were found in the interviews than in the registry. Hence, the authors' statement—that relying on case-control studies would have overestimated the effects of abortion by 50 percent—is predicated on the assumption that where the registry claims a woman has *not* procured an abortion and she states in her interview that she *has* procured an abortion, the registry is to be trusted over the woman herself.

Table 3: Breakdown of Induced Abortions as (un)Registered and (un)Reported in the 1991 Lindefors Harris Study

24 cases had abortions in the registry	26 cases reported abortions in their interview (19 were registered, 7 were not)	
5 DID NOT disclose registered abortions	19 DID disclose registered abortions	7 disclosed UNREGISTERED abortions
59 controls had abortions in the registry	44 controls reported abortions in their interview (43 were registered, 1 was not)	
16 DID NOT disclose registered abortions	43 DID disclose registered abortions	1 disclosed an UNREGISTERED abortion

In their 1994 study, Daling and colleagues note¹⁶⁷ of the 1991 Lindefors Harris study that 19 of 24 cases and 42 of 59 controls reported their *registered* abortions.¹⁶⁸ “[N]o national registry record of an abortion,” she writes, “could be located for seven other case patients, but only one other control, who claimed to have had an abortion.” (Among cases the error here in the registry is larger than the error introduced by underreporting! See the chart below.) Daling et al. state that they think it unlikely that women with no induced abortion history would claim to have had an abortion. When they recalculate the risk associated with relying on case-control studies under the assumption that overreporting did not take place, “the size of the spurious increase in risk that arises from reporting differences between case patients and controls is only 16 [percent].”

¹⁶⁷ 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.

¹⁶⁸ Lindefors Harris et al. actually show that 43 of 59 controls reported their registered abortions. See 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): 1005.

- **Minute disparity in underreporting insufficient to dismiss case-control studies.** 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*. Had 17 women instead of 19 women in the case group reported their induced abortions, a larger fraction of cases than controls would have underreported their abortions. Furthermore, when respondents are stratified by age into two groups (aged younger than 40 and aged 40 to 44), Lindefors Harris et al. find that, among those younger than 40, *cases* 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 minute difference in underreporting is insufficient as a basis for a hypothesis used to undermine all retrospective studies in a body of literature.

The 1991 Lindefors Harris study is an oft-invoked piece of research. Its findings have been referenced in many major articles, but, apart from the 1994 Daling study, they have not been challenged. Daling's recalculation of these findings directs scrutiny to claims of recall bias and shows empirically what can be deduced logically: Some women who are sick and some women who are healthy will fail to disclose socially sensitive behaviors, but the reporting differences between these two groups are not sufficient to altogether discard the results of a piece of research.

2. 1996 Rookus study

In 1996, Rookus et al. conducted a study¹⁶⁹ aimed at ascertaining the effect of induced abortion on breast cancer and at indirectly determining the role that reporting bias, or recall bias, plays in affecting the risk reported in studies. Though the authors assert that their findings provide indirect evidence that reporting bias affects the results of case-control studies, their findings are an insufficient basis for such an assertion.

The Rookus study, comprised of Dutch women, included 918 cases with invasive breast cancer identified through the Dutch Regional Cancer Registries. The women were between the ages of 20 and 54 at the time of their diagnosis, which took place between 1986 and 1989. The study also included 918 matched controls, identified through Dutch "municipal registries."

The authors assessed differences between cases and controls in demographic factors, such as age, degree of education attained, and region, as well as reproductive factors, such as age at first full-term pregnancy, number of full-term pregnancies, use of oral contraceptives, and induced abortion. The authors also controlled for family history (both first- and second-degree) of breast cancer. The authors identified the differences in these categories among aborting and non-aborting cases and controls.

¹⁶⁹ 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.

- **Neglect of some potential breast cancer risk factors.** The authors did not include controls for age at menarche, alcohol consumption, or smoking.
- **Induced abortion.** Among parous women, the authors found a significantly increased risk of breast cancer with induced abortion, adjusted for age at first-full term pregnancy, number of full-term pregnancies, family history of breast cancer, breastfeeding duration, spontaneous abortion, and injectable contraception use. Among nulliparous women, no significant association was detected between breast cancer and induced abortion.
- **Induced abortion regarding timing of first full-term pregnancy.** After adjustment for these factors, first induced abortion before first birth was also found to have a marginally significant, positive influence on breast cancer risk, relative to being parous and having no abortion history. No significant association was found between breast cancer and first abortion after first birth when controlling for the above mentioned confounding factors.
- **Age at first induced abortion.** No significant association was found between breast cancer risk and age at first induced abortion (at or before age 30, or after age 30).
- **Gestational period of first abortion.** A significant, positive influence was found on breast cancer among parous women who, in their first aborted pregnancy, had an induced abortion at or prior to eight weeks' gestation, relative to being parous and having no abortion history. No significant association was detected for a first induced abortion at later than eight weeks' gestation.
- **Spontaneous abortion.** Rookus et al. report in text that no significant association was found between breast cancer and general spontaneous abortion history, among either parous or nulliparous women. A marginally significant, positive influence was found for spontaneous abortion before a first birth.
- **Lack of distinction between first- and second-trimester spontaneous abortion.** The authors did not distinguish the effects of first-trimester and second-trimester spontaneous abortions.
- **Disparity in risk with induced abortion between regions.** The authors attempted to identify the influence of reporting bias by comparing the breast cancer risk found to be conferred by induced abortion in two different regions in The Netherlands. Should the risk found in the more religious southeastern regions exceed that found in the less religious western regions, Rookus et al. reasoned, the difference could be attributed to underreporting on the part of control patients.

The authors assert that reporting bias did affect the risk associated with induced abortion. 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. No abortion registry for the relevant period is available to corroborate or contradict the women's claims. The authors found no difference

in the risk associated with spontaneous abortions in these regions, and they found that controls in the more religious southeastern areas tended to similarly underreport oral contraceptive use (based on differing claims between women and their prescribers). In their conclusion, Rookus et al. state that their “study shows that reporting bias is a real problem and that it deserves more quantitative assessment in case-control studies that are based on information from study subjects only.”

- **No test for recall bias.** Their study’s findings are suggestive. However, though the authors’ assertion—that reporting bias contributed to the gap between the odds ratios derived in the more religious southeastern areas and less religious western areas—is plausible, they do not actually test for recall or reporting bias, and there are several problems with their assumption that reporting bias is the source of the disparity between the odds ratios.
- **No data on sample’s religiosity.** First, Rookus et al. note that 63 percent of women in the southeastern regions were Roman Catholic, compared to only 28 percent of women in the western regions. However, their study includes no data on the religious affiliation and practice of their subjects. The absence of this data undermines their suggestion that religiosity motivated differential reporting between cases and controls.
- **Omitted variable bias: religiosity (somewhat) controlled via a control for injectable contraceptive use.** Second, use of contraception is prohibited by the Roman Catholic Church. Hence, by controlling for injectable contraceptive use as they do in Table 2, the authors controlled (to an extent) for the religious devotion and the set of religious norms that might constrain someone from reporting an induced abortion. This is an omitted variable bias (in which the risk associated with the thing omitted falls onto its nearest correlate). Yet, even with this control for religiosity—and thus, for the motivation to hide abortion history cited by the authors—Table 2 shows induced abortion to have a significant, positive influence on breast cancer risk.
- **More agreement to participate among controls than cases.** Third, the authors note that 60 percent of case patients and 72 percent of control patients agreed to participate in the study. This markedly larger willingness to participate among controls seems to undermine the suggestion that controls are more likely than cases to obscure any induced abortion history, though 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.”¹⁷⁰
- **Unsuitable data collection.** Fourth, as in the case of the 1991 Lindefors Harris study, the interviews in this study were conducted in the home. This

¹⁷⁰ 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): 1760.

alone would bias the study's results away from abortion-breast cancer linkage, completely apart from differential reporting between cases and controls or religiosity-based underreporting. This also makes any connection between recall bias in this study (home interviews) and what may occur in more careful case-control studies (clinical interviews) problematic at least: the data collection environments are markedly different.

- **No clear source of risk disparity.** Fifth, as we noted above, some analyses of induced abortion and breast cancer risk produce larger risks than others, and this may be due to any number of factors. Some societies and cultures may simply expose women to fewer carcinogens, as was possibly the case in the 2006 Tehranian study in Iran or the 2011 Khachatryan study in Armenia. A generally lower number of potential carcinogenic channels (e.g., reduced consumption of alcohol, lower use of oral contraception, etc.) could show any effect conferred by induced abortion more clearly. The differing risk ratios associated with induced abortion in the more religious southeastern regions and the less religious western regions may be due to any number of factors; hence, there is no need for the assertion of reporting bias as it is put forward but not substantiated by the authors.

3. Summary

It is assumed that some fraction of study participants will fail to disclose socially sensitive behaviors. We have seen in some studies that women state abortions were spontaneous when official register reports indicate that they were induced abortions. It may be that women interviewed in their homes or over the phone tend more than women interviewed in clinical settings not to disclose induced abortions. Can it be said with certainty that controls will more often fail to disclose their abortions than cases? The “sobering” effect that breast cancer supposedly has on cases—the desire to disclose all possible sources of illness—is plausible as a hypothesis, but, unproven, it cannot be used to dismiss findings of significance. Lindefors Harris et al. attempted to demonstrate that cases disclosed induced abortions significantly more often than controls did and failed.

We also do not have evidence that more religious controls tend to hide abortion history. Rookus et al. attempted to demonstrate this and failed. (As an aside, Daling et al. control for religion in their analyses of induced abortion and still detect a significant effect.¹⁷¹) However, controls for recall bias may be constructed to ensure recall bias does not affect results. Additionally, as we have noted above, Melbye et al.¹⁷² controlled for the period in which induced abortions were procured in their analyses. An assessment of the relationship between the legality of induced abortion and breast cancer incidence

¹⁷¹ 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): 1588-1589.

¹⁷² 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.

is an excellent test of induced abortion's effects without any potential effect of reporting bias.

Additionally, Daling et al. attempted to determine if reporting bias affected their analysis by assessing the influence of induced abortion on cervical cancer risk. No effect was detected for induced abortion on cervical cancer risk. Hence, as Daling et al. note, "Unless a history of an induced abortion were truly negatively associated with the incidence of invasive cervical cancer, this result argues against their being differential reporting of prior induced abortions by cancer case patients and controls...."¹⁷³

In the absence of firm data regarding whether cases disclose more socially sensitive behaviors than controls, we must ask a larger question: Can scientists trust study participants to accurately report their own medical histories? If not, then many commonly-referenced sources of medical information are inappropriate for use in scientific studies. However, as in the case of Lindefors Harris et al., even official government registries may not be completely accurate and may introduce error into calculations.

Regardless, if researchers are to trust medical histories as reported by individuals, they must do so without discrimination, until it has been scientifically demonstrated that certain cohorts systematically report their medical histories inaccurately. Neither the 1991 Lindefors Harris study nor the 1996 Rookus study shows this. The results of case-control studies must not be dismissed out of hand.

IV. The National Cancer Institute

The National Cancer Institute (NCI) was founded in 1937 under the National Cancer Institute Act. It is "the Federal Government's principal agency for cancer research and training."¹⁷⁴

The NCI concluded that induced abortion poses no increased risk of breast cancer, based upon the consensus of the workshop they convened in 2003. As we have explained above, this assertion contradicts well-known reproductive risks for breast cancer for certain women. These risks are acknowledged in standard texts.¹⁷⁵ NCI's assertion also contradicts the 18 epidemiologic studies and two ecological epidemiological studies from around the world noted above.

Having reviewed the variance in method quality and the findings of many studies in the literature on the relationship between induced abortion and breast cancer, we will now review some guidelines for establishing causality in research before addressing next steps for the field.

¹⁷³ Daling et al., *supra* note 171, at 1584-1592.

¹⁷⁴ National Institutes of Health, National Cancer Institute, NCI Mission Statement, National Cancer Institute. <http://www.cancer.gov/aboutnci/overview/mission> (accessed October 1, 2012).

¹⁷⁵ Reproductive risks that are acknowledged include preterm birth before 32 weeks, delay of full term pregnancy, nulliparity. For medical texts, *see supra*, note 3.

V. The Bradford Hill Causality Guidelines

In 1965, Sir Austin Bradford Hill put forward¹⁷⁶ the following nine characteristics as a means of assessing the nature of a relationship between a potential risk factor and a disease. These nine features are not a cut and dried checklist; as Sir Bradford Hill noted, “None of my nine viewpoints can bring indisputable evidence for or against the cause-and-effect hypothesis and none can be required as a *sine qua non*. What they can do, with greater or less strength, is to help us make up our minds on the fundamental question—is there any other way of explaining the set of facts before us, is there any other answer equally, or more, likely than cause and effect?”

1. **Strength [of association]**. The strength of the association between the two factors can be indicative of a causal association. Sir Bradford Hill notes that chimney sweeps had 200 times the mortality due to scrotal cancer of other workers. He also notes that cigarette smokers had nine or 10 times the mortality due to lung cancer of non-smokers (and that heavy smokers had 20 to 30 times the lung cancer mortality of non-smokers).
2. **Consistency**. Sir Bradford Hill states that an observed relationship between two factors should be made with some consistency. “Has it been repeatedly observed by different persons, in different places, circumstances, and times?” Out of 72 epidemiological studies we have reviewed on the link between induced abortion and breast cancer, 21 show some positive, statistically significant relationship. Seven studies show a positive, marginally significant link between induced abortion and breast cancer. Of three meta-analyses on the subject, two show a positive, statistically significant link between induced abortion and breast cancer. Two ecological epidemiological studies show a relationship between induced abortion and breast cancer. These studies have been conducted over fifty years across multiple cultures and countries—from Japan, China, and Iran to Germany, the UK, and the United States.
3. **Specificity [of cause]**. Specificity of cause—“one-to-one relationships,” as Sir Bradford Hill calls them—is rare. Where it occurs, it may imply causality, but he notes that “diseases may have more than one cause.” Some specificity of cause for breast cancer—hormone exposure—is apparent; what may vary among women is the channel of exposure (e.g., induced abortion, oral contraceptive use).
4. **Temporality**. The hypothesized cause must precede the outcome. The exposure to the supposed risk must occur before the disease is detected; in the case of the abortion-breast cancer link, the abortion must occur before the breast cancer forms.
5. **Biological gradient (i.e., a dose effect)**. If a factor is causal of a disease, then (based on biological mechanisms) increased exposure to that factor

¹⁷⁶ Austin Bradford Hill, “The Environment and Disease: Association or Causation?” *Proceedings of the Royal Society of Medicine* 58 (1965): 295-300.

ought to increase one's risk of the disease. In the case of cigarettes, we now know that the more cigarettes one smokes, the higher is one's risk of lung cancer. The longer a woman is pregnant before an abortion, the more immature breast tissue forms up to 20 weeks of pregnancy, and the higher her risk of breast cancer will be. Despite its flaws, the 1997 Melbye study found a statistically significant risk increase with induced abortions after 18 weeks' gestation, relative to induced abortions at nine to 10 weeks' gestation.

Furthermore, though just one exposure to asbestos can cause mesothelioma to form and one induced abortion may induce the formation of breast cancer, there is evidence that increasing the number of induced abortions one obtains also increases one's breast cancer risk. This is called a dose effect outcome.¹⁷⁷

However, as Sir Bradford Hill notes, "[t]he comparison would be weakened, though not necessarily destroyed, if it depended upon... a much heavier death rate in light smokers and a lower rate in heavier smokers. We should then need to envisage some much more complex relationship to justify the cause and effect hypothesis."

6. **Plausibility.** The biological mechanism that explains the reason for the risk association ought to be plausible, though, as Sir Bradford Hill explained, "[w]hat is biologically plausible depends upon the biological knowledge of the day."

The breast physiology that explains the risk of breast cancer with induced abortion is thoroughly explained in Section II and is supported by standard medical texts. Elevated levels of estrogen during pregnancy leave the breast with increased numbers of cancer-vulnerable Type 1 and Type 2 lobules. If the pregnancy does not continue to 32 weeks, the breast is left with more lobules vulnerable to cancer. If the pregnancy does continue to 32 weeks, sufficient breast tissue matures into cancer-resistant Type 4 lobules that a woman is protected against breast cancer. Furthermore, it has been shown that the longer a woman is pregnant before an induced abortion, the higher is her risk of breast cancer.¹⁷⁸ This same physiology can account for other well-accepted reproductive risks of breast cancer, such as nulliparity (childlessness), premature delivery before 32 weeks, and second-trimester miscarriages.

7. **Coherence.** The hypothesis, when proven, should not do violence to related sets of scientific findings but fit in with them. The association of breast cancer and abortion is in accord with the known natural history and biology of breast cancer. The biological hypothesis of the induced abortion-breast cancer link is consistent with other reproductive protective factors, including full-term pregnancy, early age (around age 20) at first full-term pregnancy, lower pro-

¹⁷⁷ 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.

¹⁷⁸ 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. After 32 weeks, of course, the risk of breast cancer declines sharply.

lactin levels in parous women (women who have given birth), and lower risk with each full-term pregnancy. The biological hypothesis is also consistent with known reproductive risk factors such as nulliparity (childlessness), late age at first full-term pregnancy (age 30 and later), and premature delivery before 32 weeks.

8. **Experiment.** Sir Bradford Hill notes that experimental evidence of the relationship between a potential risk factor and a disease is sometimes possible to obtain, and it may show “the strongest support for the causation hypothesis.” Two pathologists studied the effect of a breast carcinogen (DMBA) given to groups of rats. The aborting rats developed breast cancers at a higher rate when given DMBA than did the rats that had pups, or even the virgin rats.¹⁷⁹ This is all quite in line with the microbiology of human breast cancer findings (see Section II).
9. **[By] analogy.** Similar exposures may result in similar effects. For example, heavy exposure to cigarette smoking causes bladder cancer as well as lung cancer. Premature delivery before 32 weeks increases breast cancer risk, because the breasts are left with more lobules where breast cancers can start, and an induced abortion is similar to a delivery before 32 weeks’ gestation in its effects on the breast.¹⁸⁰ Additionally, increased estrogen exposure—early menarche, late menopause, estrogen/progesterone use (so-called “hormone replacement therapy”), hormonal contraceptive use, and healthy pregnancy not carried to 32 weeks—exerts similar influence on the body, no matter the form of exposure.

More modern means for determining causality include natural experiments, population shifts, instrument variables, and randomized assignment.¹⁸¹ Regardless, this review of Sir Bradford Hill’s guidelines is a useful exercise: We see that many studies of induced abortion demonstrate significant associations, across multiple cultures and with some apparent specificity of cause (hormone exposure). The association manifests itself in the appropriate order, demonstrates a dose effect, is biologically plausible and coherent with existing science, and has been demonstrated by analogy.

VI. Proposed Research Agenda

The breast is a most difficult organ to study, as its susceptibility varies throughout a woman’s life. Her risk of breast cancer is dependent upon whether she has had a long or short susceptibility window and whether her breast’s lobules have matured and

¹⁷⁹ Jose Russo and Irma H. Russo, “Susceptibility of the Mammary Gland to Carcinogenesis. II. Pregnancy Interruption as a Risk Factor in Tumor Incidence,” *American Journal of Pathology* 100, no. 2 (1980): 497-512.

¹⁸⁰ 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.

¹⁸¹ Marriage and Religion Research Institute, “Causal Determination for Social Policy: Counterfactuals, Natural Experiments, Population Shifts, by Henry Potrykus (February 7, 2013), 2; <http://marri.us/causality> (accessed July 18, 2013).

become relatively cancer-resistant through a pregnancy lasting longer than 32 weeks. Her risk of breast cancer will also vary according to when in her reproductive life she was exposed to that risk.

This difficulty can best be illustrated by the results of the studies regarding the carcinogenicity of cigarettes on the breast. Initially, researchers found cigarette smoking increased, decreased, or had no effect on breast cancer incidence. With the publication of a study¹⁸² that took into account both the parity and menopausal status of women, it became clear why there had been such disparity across previous studies. Nulliparous premenopausal women who smoked had a nearly tenfold increase in risk, relative to parous premenopausal women who smoked. This increase was presumably due to the toxicity of benzopyrenes, and it was much higher in nulliparous women who did not benefit from the risk reduction of a full-term pregnancy.¹⁸³ Parous postmenopausal women actually showed a decrease in risk, presumably due the nicotine metabolite, cotinine, which acts as an aromatase enzyme inhibitor, and other factors decreasing their exposure to estrogen, such as an earlier age of menopause in women who smoke. Thus, the *results of the studies on risk factors may be inconsistent and vary when reproductive history is not taken into account.*

A simplified research data collection tool and risk assessment form has been developed and used by the first author for the last 20 years and by a breast center with which she is affiliated for the last 5 years (see Appendix B).

Given the lack of a large volume of high-quality data on breast cancer in the United States, and given the disparate levels of rigor of method employed by many researchers, the need for improvement in data and research quality is clear. The breast cancer data network described below would permit research of all potential breast cancer risk factors by creating a database that would take into account the maturity and cancer-resistant state of the breast when exposed to the risk being studied. Additionally, the proposed guidelines, if implemented, could do much to improve the quality of the research in the abortion-breast cancer field.

A. Develop a National Breast Cancer Data Network

1. Develop a standardized data collection network.

A research data network could be built from existing breast centers, which are FDA-regulated and which are accredited by the National Accreditation Program of Breast Centers. These centers perform mammography screening and non-invasive breast biopsies, and routinely collect medical histories from their patients to aid in their interpretation of mammograms. This data collection could be made both comprehensive and uniform by standardizing the history taken at the time of the annual mammogram with a reproductive, hormonal, and breast history form that included all potential risk

¹⁸² P.R. Band, N.D. Le, R. Fang, M. Deschamps, "Carcinogenic and endocrine disrupting effects of cigarette smoke and risk of breast cancer," *Lancet* 360, no. 9339 (October 5, 2002): 1044-1049.

¹⁸³ I.H. Russo, "Cigarette smoking and risk of breast cancer in women," *Lancet* 360, no. 9339 (October 5, 2002): 1033-1034.

factors for breast cancer, including the variables discussed in this paper.¹⁸⁴ The data gathered would also include other potential carcinogens, such as cigarette smoking, and endocrine disrupting chemicals, such as Bisphenol A. This standardized form would be updated with each mammogram. An example form (used by a mammography center in New Jersey) can be viewed in Appendix B.

Such a standardized form, used throughout the national mammography network, would make a large database available for many breast cancer research projects, including prospective epidemiologic studies and longitudinal studies. It would also facilitate research to confirm the results of previous studies and to parse out the interactive effects of different factors.

The addition of a tissue bank could be a great asset for the furtherance of research, as breast centers already perform tissue biopsies that require follow-up by the FDA. By entering the results of the biopsy—not only of whether or not the tissue was benign or malignant, but whether or not there was benign non-proliferative or proliferative disease, such as high risk lesions (radial sclerosing lesions, papillomas, atypical hyperplasias etc.)—the results could be compared with different exposures to carcinogens and with the patient's reproductive history. One Chinese study¹⁸⁵ examining the subtypes of cancer found a statistically significant association between induced abortion and luminal A cancers. A comprehensive database would permit breast cancer subtypes to be correlated with specific reproductive or other risks.

¹⁸⁴ These factors could 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:** Personal 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.

¹⁸⁵ Peng Xing, Jiguang Li and Feng Jin, “A Case-Control Study of Reproductive Factors Associated with Subtypes of Breast Cancer in Northeast China,” *Medical Oncology* 27, no. 3 (2009): 926-931.

2. Probable sample size.

Average-sized breast centers screen 8,000 to 10,000 women per year. There are hundreds of approved National Accreditation Program Breast Centers in all 50 states.¹⁸⁶ Additionally, about 10 percent of women who undergo mammograms will be called back for more imaging tests, but only 8 to 10 percent of those women will need a biopsy. Eighty percent of biopsies show benign results.¹⁸⁷ Of every 1,000 mammograms, only around two to four end in a woman being diagnosed with breast cancer.¹⁸⁸ Hence, a database generated through these breast centers would yield a large and continuously growing dataset of cases and controls. Though this data set would be predominately limited to women 40 years old or more (the age at which regular mammograms begin), it will permit the execution of a research agenda of the highest quality.

B. Execute a Comprehensive, Sophisticated Research Agenda Using the Network Database

We have identified multiple biases and problems that may appear in the induced abortion-breast cancer literature (see Section III, A). Researchers should endeavor to avoid introducing these into their analyses. Additionally, we have suggested several research projects to execute with the large dataset that the proposed breast center network would generate.

1. How to avoid common biases and problems

- **Ensure data are properly obtained.** 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, as opposed to being conducted over the phone or in the home.
- **Avoid health or survivor bias.** At best, studies should commence with women who procure an induced abortion and follow their health for, at minimum,

¹⁸⁶ American College of Surgeons, "National Accreditation Program for Breast Centers," American College of Surgeons; <http://napbc-breast.org/resources/find.html> (accessed January 23, 2013).

¹⁸⁷ American Cancer Society, "Diagnostic mammograms investigate possible problems," Mammograms and Other Breast Imaging Procedures, last modified February 7, 2013; <http://www.cancer.org/treatment/understandingyourdiagnosis/examsandtestdescriptions/mammogramsandotherbreastimagingprocedures/mammograms-and-other-breast-imaging-procedures-types-of-mammograms> (accessed October 1, 2013).

¹⁸⁸ American Cancer Society, "What to expect when you have a mammogram," Mammograms and Other Breast Imaging Procedures, last modified February 7, 2013; <http://www.cancer.org/treatment/understandingyourdiagnosis/examsandtestdescriptions/mammogramsandotherbreastimagingprocedures/mammograms-and-other-breast-imaging-procedures-having-a-mammogram> (accessed October 1, 2013).

Note that the fraction of mammograms that leads to breast cancer diagnosis may vary, depending on the radiologist in question and their positive predictive value statistics (i.e., how many cancers are found when they call for a biopsy), which depend upon how many cancers they are afraid to miss. Because missing a cancer is a highly undesirable event and a common malpractice claim (i.e., delay of diagnosis), some radiologists have a very low threshold for biopsy. The lower the threshold, the more biopsies are performed, and the smaller is the fraction of biopsies resulting in a diagnosis of breast cancer. This varies according to geography, institution, and population.

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 ability to skew their study's results, by not excluding women with (or with a previous history of) invasive or *in situ* breast cancer and by limiting their analysis to women still in their reproductive years or just past them. Researchers should also not exclude women who die of breast cancer. As in the Naieni study, the relatives or friends of such women can be interviewed.

- **Choose correct time frames to assess induced abortion's effects.** Studies should follow women for an adequate period of time after their induced abortions—a minimum of eight to 10 years—for any resulting breast cancer to grow to a detectable size. Additionally, when studies design their analyses, their regressions' categories should be bounded so as to 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 14 years after, and 15 to 22 years).
- **Sophisticated analysis of induced abortions.** Rather than disregarding the differences between women with different reproductive histories, advanced research should be parsing out the effects of these differences. Researchers ought to 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, maternal age at induced abortion(s), and the gestational period in which induced abortions took place.
- **Standardized reference group for suitable comparisons.** 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, of the effects of repeated induced abortions, of maternal age at induced abortion, and of gestational period at induced abortion, the preferred reference group is women who have had no abortions or second-trimester miscarriages.

It is important to note that women *should not* be divided by parity status: To compare nulliparous aborting women only to nulliparous never-pregnant women will mute the effects of induced abortion, because never-pregnant women have a greater risk of breast cancer than women who have experienced full-term pregnancy.

- **Avoid reporting difficulties surrounding abortion law changes.** 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.

- **Build a fully-specified model.** Studies should avoid introducing omitted variable bias into their models by including all potential breast cancer risk factors. Researchers should not, for example, exclude data on spontaneous abortion because their focus is induced abortion.

A complete model of potential breast cancer 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; **Breast-feeding:** 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:** Personal 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.
- **Distinguish consistently between induced and spontaneous abortions.** Most studies distinguish between induced and spontaneous abortions in their general analysis, but many fail to do so in their analyses of (for example) the influence of abortion timing relative to first full-term pregnancy or of the influence of repeated abortions. An analysis that does not so distinguish is of very limited use to the reader.

- **Avoid publication bias.** Meta-analyses and re-analyses ought not to exclude studies for unscientific reasons. They also ought not to dismiss retrospective data, even where they contradict prospective data, *merely because* they are retrospective data. As we explained in our section on recall bias (Section III, E), it is far from certain that controls underreport induced abortions at a greater rate than cases.
- **Ensure samples represent the general population.** A study ought to ensure that its sample is representative of the general population in order to ensure that its results will be generalizable to the general population. If a sample contains only urban women, or only white women, or only women with greater-than-average levels of educational attainment, its results can only be fairly applied to these women and not to all women.
- **Ensure samples are of adequate size.** Researchers ought not to employ too-small samples; this will enable them to distinguish women across as many categories (e.g., different parity statuses, differently timed induced and spontaneous abortions) as necessary without generating categories too small for any “signal” to be perceptible over fluctuations from other sources of error.
- **Distinguish between first- and second-trimester spontaneous abortions.** Studies must distinguish between the two very different types of miscarriage (first-trimester vs. second-trimester), whenever the available data make it possible. As noted earlier, these have different effects on breast cancer risk due, ordinarily, to different causes.
- **Completely explain model employed.** Researchers should not leave the reader without a clear explanation of their methods. Authors should note, for example, exactly which women are included in a given category, and what means (statistical processes) they used to derive their figures.

Though many of these problems may be simple human error, an article that appeared in *Nature* in 2005 showed that around 20 percent of mid-career scientists and 10 percent of early-career scientists had “chang[ed] the design, methodology or results of a study in response to pressure from a funding source.”¹⁸⁹ The over 3,000 scientists surveyed were funded by the National Institutes of Health, of which the National Cancer Institute is a part. Congress would do well to increase its oversight of federal grant recipients in order to protect these scientists and their work from institutional pressure.

2. Studies to conduct

The database generated by the proposed breast cancer center network would permit the elimination of major gaps in the research literature. We note here some research topics that could be covered with the databases our proposals would make available.

As an aside, we would urge that all epidemiologists and university-affiliated research clinicians have access to this database so that no organization or institute may control

¹⁸⁹ Brian C. Martinson, Melissa S. Anderson, and Raymond de Vries, “Scientists behaving badly,” *Nature* 435, no. 9 (2005): 737-738.

the direction of the research. Such openness would eliminate personal, institutional, ideological, and funding-source bias, improve transparency, and facilitate the practice of replication (and the expectation of replication when results are controversial), all of which are likely to improve research quality.

- **Execute an updated meta-analysis.** The studies currently in existence ought to be reevaluated in a new meta-analysis. Joel Brind's 1996 meta-analysis,¹⁹⁰ Valerie Beral's 2004 meta-analysis,¹⁹¹ and Yubei Huang's 2013 meta-analysis¹⁹² were published with very different conclusions; Beral's analysis, as we have noted above, contained many methodological errors and biases. Since their publication, many additional studies have been published across the world. A meta-analysis of the extant studies would help to clarify the independent link between induced abortion and breast cancer.
- **Early-age induced abortion and duration until first full-term pregnancy.** The disparate risks arising from differing time periods between early, aborted first pregnancies and first full-term pregnancy (if any) merit greater attention than they have received, especially given that 18 percent of induced abortions performed in the U.S. in 2008 were to those 20 and younger,¹⁹³ and almost half of first induced abortions between 2006 and 2010 were reportedly to teenagers.¹⁹⁴
- **Late-age induced abortion.** The data seem to show that women who procure induced abortions after 30 are at increased risk of breast cancer.¹⁹⁵ More research is needed to ascertain whether this is the case and, if so, how large is the risk conferred by induced abortion at this age.
- **Duration between induced abortion(s) and (first) full-term pregnancy.** Daling et al.'s finding about the benefit of breastfeeding fewer than 10 years

¹⁹⁰ Joel Brind, Vernon M. Chinchilli, Walter B. Severs, and Joan Summy-Long, "Induced Abortion as an Independent Risk Factor for Breast Cancer: A Comprehensive Review and Meta-Analysis," *Journal of Epidemiology and Community Health* 50, no. 5 (1996): 483-484.

¹⁹¹ 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.

¹⁹² 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.

¹⁹³ Gilda Sedgh, Akinrinola Bankole, Susheela Singh, and Michelle Eilers, "Legal Abortion Levels and Trends By Woman's Age at Termination," *International Perspectives on Sexual and Reproductive Health* 38, no. 3 (September 2012): 144; <http://www.guttmacher.org/pubs/journals/3814312.pdf> (accessed July 5, 2013).

¹⁹⁴ Marriage and Religion Research Institute, *Demographics of Women Who Have Had an Abortion: from the National Survey of Family Growth 2006-2010*, by Patrick Fagan and Scott Talkington (2013): 8; www.marri.us/abortion-demographics (accessed August 7, 2013).

¹⁹⁵ 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): 1588; F. Fioretti, A. Tavani, C. Bosetti, C. La Vecchia, E. Negri, F. Barbone, R. Talamini, and S. Franceschi, "Risk factors for breast cancer in nulliparous women," *British Journal of Cancer* 78, no. 11/12 (1999): 1925.

after an induced abortion¹⁹⁶ is suggestive of possible benefits of *birth* soon after induced abortion. Any risk reduction associated with full-term pregnancy after an induced abortion needs to be clarified, among parous and nulliparous women of all ages, with respect to the duration of time between the induced abortion and the birth.

- **Oral contraceptive use and induced abortion.** Another gap in the literature is differing breast cancer risks associated with differing levels of oral contraceptive use (high intake of progesterone and/or estrogen, both implicated in speeding up mitosis and shortening the time for repairing DNA mutations) before or after an induced abortion.¹⁹⁷
- **Repeated full-term pregnancy and repeated induced abortion.** The database would also permit research on the different levels of protection provided by different numbers of full-term pregnancies before an abortion and the potential attenuation of this protective effect with repeated abortions.
- **Gestational period at induced abortion.** Attention also ought to be devoted to the difference in rates of breast cancer development according to the stage of gestation at which abortions are procured.
- **The nature of the induced abortion-breast cancer link.** More research ought to be devoted to the *nature* of the relationship between induced abortion and breast cancer. 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. We have here written our critiques and suggestions under this assumption, but this is a gap in the literature that ought to be filled.

VII. Conclusion

Our overview of the research and of advances in the biology of breast development show different magnitudes of breast cancer risk following a procured abortion. The independent effect of induced abortion on breast cancer risk as demonstrated in epidemiological studies varies from small to large and from nonsignificant to marginally or highly significant, depending on myriad factors now known to affect these rates.

Though the independent effect of induced abortion is not always statistically large, it is important to consider the overall influence that abortion has in shaping one's repro-

¹⁹⁶ 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.

¹⁹⁷ Because induced abortion will leave a childless woman with more undifferentiated breast tissue than a woman who has never been pregnant, one might expect those women taking oral contraceptives after an induced abortion to be at higher risk for breast cancer than a woman who does not take them after an abortion.

ductive history. The single effect of induced abortion on breast cancer risk is trumped by the overall effect of a long-term avoidance of pregnancy. In this lifestyle pattern, the effects of late age at first full-term pregnancy or nulliparity, oral contraceptive use, and induced abortion (possibly while nulliparous or long before first birth, if any) could all be evident and working in concert to increase a woman's breast cancer risk. Additionally, whereas a woman cannot control some aspects of her risk of breast cancer—for example, genetic mutations—induced abortion is a modifiable risk. For instance, adoption alternatives would permit the mother to experience full-term pregnancy's risk reduction, which may be important to women who have a high risk of breast cancer for other reasons, while shortening the waiting times of adoptive parents. As stated in a major text, "Nevertheless, a social norm that encouraged carefully planned first pregnancies at the beginning of advanced education and career development would reduce breast cancer rates."¹⁹⁸

Women also need the opportunity for informed consent when choosing a surgical procedure that will elevate breast cancer risk, a leading cause of cancer death in women. Women who choose induced abortion should be made aware of their increased risk, so that they can be deliberately screened at an appropriate time and through early detection find more curable cancers. If the abortion occurs at a young age, when breast tissue is very dense, more appropriate screening with the use of ultrasound and MRI in addition to mammograms could be offered earlier than the age at which screening is standard, which is normally age 40. Ten years after an induced abortion would be an appropriate time to start this early screening.

By understanding the impact of all risk factors and obtaining an accurate estimate of risk, screening mammography could be more appropriately used for those women at increased risk, while reducing screening for those at low risk. At this time in medical history, when cost effectiveness is of great concern and when premenopausal *in situ* and Stage 4 breast cancers have been increasing, identifying women who are at increased risk of breast cancer and require early screening is of the utmost importance.

Furthermore, 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, oral contraceptive use, and "hormone replacement therapy," or on the protective effect of having multiple full-term pregnancies. The increased risk posed or protection offered by these events all operate through the channel of hormone exposure. That the aforementioned protections, vulnerabilities, or exposures affect breast cancer

¹⁹⁸ Walter C. Willett, Beverly Rockhill, Susan E. Hankinson, David J. Hunter, and Graham A. Colditz, Chapter 15: "Epidemiology and Nongenetic Causes of Breast Cancer," in *Diseases of the Breast*, eds. Jay R. Harris, Marc E. Lippman, Monica Morrow, and C. Kent Osborne, 2nd ed. (Philadelphia: Lippincott Williams & Wilkins, 2000), 212.

risk is little debated. As Jiang et al. assert, “[b]reast cancer is a hormone-related cancer.”¹⁹⁹ Hence, the debate surrounding the relationship between induced abortion—another means of exposure to high hormonal levels not mitigated by cell differentiation—and breast cancer is incongruous.

Though it is difficult for medical research to be free from the influence of ideological agendas, science advances only by being open to data that are contrary to treasured hypotheses. This is the very means of the constant revolution in science and to new insights in all its branches. New medical breakthroughs discovered by scientists throughout history have often been difficult to accept, even when they were not as politically and morally charged as the subject of this article. However, we hope we have mapped out a way for breast cancer science to move forward that those in the medical and academic community will find appealing.

Acknowledgement: The authors would like to thank Irma H. Russo, M.D., and David Prentice, Ph.D., for their invaluable help with reviewing and making suggestions regarding the content of this article.

¹⁹⁹ 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=MzMtMzUgMTluMiZrY29kZT0yNzAxJmZubz0w&rpqubun=i (accessed December 7, 2012).

Appendix A: Studies of the relationship between abortion and breast cancer that differentiate between induced and spontaneous abortion and three meta-analyses

Studies		No.	Year	Reference	OR or RR (95% CI)	Statistically Significant	Positive or Negative Correlation	Country or Population
	1	1957	M. Segi, I. Fukushima, S. Fujisaku, M. Kurihara, S. Saito, K. Asano, and M. Kamoi, "An Epidemiological Study on Cancer in Japan," <i>Japanese Journal of Cancer Research (GANN)</i> 48 (Suppl.): 1-63.	2.63 (1.85-3.75)*	Yes	Positive	Japan	
	2	1968	H. Watanabe and T. Hirayama, "Epidemiology and Clinical Aspects of Breast Cancer," <i>Nippon Rinsho</i> 26 (1968): 1843-1849 (in Japanese).	1.51 (0.91-2.53)*	No	Positive	Japan	
	3	1978	V.V. Dvoirin and A.B. Medvedev, "Role of Women's Reproductive Status in the Development of Breast Cancer," in <i>Methods and Progress in Breast Cancer Epidemiology Research</i> , by Tallin (Moscow: Oncology Science Center of the USSR Academy of Sciences, 1978), 53-63 (in Russian).	1.71 (0.80-3.64)*	No	Positive	USSR/Estonia	
	4	1979	B. Burany, "Gestational characteristics in women with breast cancer," <i>Jugosl/Ginekol Opstel</i> 19 (1979):237-247 (in Serbo-Croatian).	0.50 (0.33-0.74)*	Yes	Negative	Yugoslavia	
	5	1981	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," <i>British Journal of Cancer</i> 43, no. 1 (1981): 72-76.	2.37 (0.85-6.93)*	No	Positive	United States	
	6	1982	F. Nishiyama, "The Epidemiology of Breast Cancer in Tokushima Prefecture," <i>Shikoku tchi</i> 38 (1982): 333-343 (in Japanese).	2.52 (1.99-3.20)*	Yes	Positive	Japan	
	7	1983	L.A. Brinton, R. Hoover, and J.F. Fraumeni, Jr., "Reproductive factors in the aetiology of breast cancer," <i>British Journal of Cancer</i> 47, no. 6 (1983): 757-762.	1.34 (3-5.6) if before first live birth; .89 (4-2.00) if after first live birth; 5.5 (.8-36.8) if nulliparous	No	Positive/Negative/Positive	United States	
	8	1984	Monique G. Lé, Annie Bachelot, F. Doyon, A. Kramer, and Catherine Hill, "Oral Contraceptive Use and Breast or Cervical Cancer: Preliminary Results of a French Case-Control Study," in <i>Hormones and Sexual Factors in Human Cancer Aetiology</i> , eds. J.P. Wolff and J.S. Scott (Amsterdam: Elsevier, 1984), 139-147.	1.32 (0.97-1.77)*	No	Positive	France	
	9	1985	T. Hirohata, T. Shigematsu, A.M. Nomura, Y. Nomura, A. Horie, and I. Hirohata, "Occurrence of breast cancer in relation to diet and reproductive history: a case-control study in Fukuoka, Japan," <i>National Cancer Institute Monograph</i> 69 (1985): 187-190.	1.52 (0.93-2.48)	No	Positive	Japan	

10	1987	C. La Vecchia, A. Decarli, F. Parazzini, A. Gentile, E. Negri, G. Cecchetti, and S. Franceschi, "General epidemiology of breast cancer in northern Italy," <i>International Journal of Epidemiology</i> 16, no. 3 (1987): 347-355.	1.19 (0.82-1.71) if 1 IA; .78 (.52-1.13) if ≥ 2 IA	No	Italy
11	1988	M. Ewertz and S.W. Duffy, "Risk of breast cancer in relation to reproductive factors in Denmark," <i>British Journal of Cancer</i> 58, no. 1 (1988): 99-104.	3.85 (1.08-13.6) with IA in nulliparous women	Yes	Denmark
12	1988	E. Luporsi, "Breast cancer and alcohol," (PhD thesis, University of Paris-Sud, 1988), data in N. Andrieu, S.W. Duffy, T.E. Rohan, M.G. L�, E. Luporsi, M. Gerber, R. Renaud, D.G. Zaridze, Y. Lifanova, and N.E. Day, "Familial Risk, Abortion and Their Interactive Effect on the Risk of Breast Cancer—A Combined Analysis of Six Case-Control Studies," <i>British Journal of Cancer</i> 72, no. 3 (1995): 744-751.	1.8 (1.0-3.5) if 1 IA; 1.9 (.5-6.9) if ≥ 2 IA	Marginal/No	France
13	1988	D.G. Zaridze data (unpublished) in N. Andrieu, S.W. Duffy, T.E. Rohan, M.G. L�, E. Luporsi, M. Gerber, R. Renaud, D.G. Zaridze, Y. Lifanova, and N.E. Day, "Familial Risk, Abortion and Their Interactive Effect on the Risk of Breast Cancer—A Combined Analysis of Six Case-Control Studies," <i>British Journal of Cancer</i> 72, no. 3 (1995): 744-751.	1.0 (.7-1.4) if 1 IA; .7 (.6-1.0) if ≥ 2 IA	No/Marginal	Russia
14	1984	M.G. L�, A. Bachelot, F. Doyon, A. Kramar, and C. Hill, "Oral Contraceptive Use and Breast Cancer or Cervical Cancer: Preliminary Results of a French Case-Control Study," in <i>Hormones and Sexual Factors in Human Cancer Aetiology</i> , eds. J-P Wolff and J.D. Scott (Amsterdam: Elsevier Science, 1984), data in N. Andrieu, S.W. Duffy, T.E. Rohan, M.G. L�, E. Luporsi, M. Gerber, R. Renaud, D.G. Zaridze, Y. Lifanova, and N.E. Day, "Familial Risk, Abortion and Their Interactive Effect on the Risk of Breast Cancer—A Combined Analysis of Six Case-Control Studies," <i>British Journal of Cancer</i> 72, no. 3 (1995): 744-751.	1.2 (.7-2.1) if 1 IA; 1.9 (1.0-3.6) if ≥ 2 IA	No/Marginal	France
15	1988	T. Rohan, A.J. McMichael, and P.A. Baghurst, "A population-based case-control study of diet and breast cancer in Australia," <i>American Journal of Epidemiology</i> 128 (1988): 478-489, data in N. Andrieu, S.W. Duffy, T.E. Rohan, M.G. L�, E. Luporsi, M. Gerber, R. Renaud, D.G. Zaridze, Y. Lifanova, and N.E. Day, "Familial Risk, Abortion and Their Interactive Effect on the Risk of Breast Cancer—A Combined Analysis of Six Case-Control Studies," <i>British Journal of Cancer</i> 72, no. 3 (1995): 744-751.	2.7 (1.1-6.7) if 1 IA; 2.2 (.4-12.0) if ≥ 2 IA	Yes/No	Australia
16	1988	Lynn Rosenberg, Julie R. Palmer, David W. Kaufman, Brian L. Strom, David Schottenfeld, and Samuel Shapiro, "Breast Cancer in Relation to the Occurrence and Time of Induced and Spontaneous Abortion," <i>American Journal of Epidemiology</i> 127 (1988): 981-989.	1.2 (.9-1.6) if parous; 1.3 (.8-2.2) if nulliparous	No	United States

17	1989	B.M. Lindfors Harris, G. Eklund, O. Meirik, L.E. Rutqvist, and K. Wiklund, "Risk of cancer of the breast after legal abortion during first trimester: a Swedish register study," <i>British Medical Journal</i> 299, no. 6713 (1989): 1430-1432.	0.77 (0.58-0.99)	Yes	Negative	Sweden/ Norway
18	1989	Holly L. Howe, Ruby T. Senie, Helen Bzduch, and Peter Herzfeld, "Early Abortion and Breast Cancer Risk Among Women Under Age 40," <i>International Journal of Epidemiology</i> 18 (1989): 300-304.	1.9 (1.2-3.0)	Yes	Positive	United States
19	1989	Larissa I. Remennick, "Reproductive Patterns and Cancer Incidence in Women: A Population-Based Correlation Study in the USSR," <i>International Journal of Epidemiology</i> 18, no. 3 (September 1989): 498-510.	data not in form of OR	Yes	Positive	USSR
20	1990	H.O. Adami, R. Bergström, E. Lund, and O. Meirik, "Absence of association between reproductive variables and the risk of breast cancer in young women in Sweden and Norway," <i>British Journal of Cancer</i> 62, no 1 (1990): 122-126.	0.8 (0.5-1.1) if 1 IA; 1.3 (0.6-3.0) if ≥ 2 IA	No	Negative/Positive	Sweden/ Norway
21	1991	Fabio Parazzini, Eva Negri, and Carlo La Vecchia, "Spontaneous and induced abortions and risk of breast cancer," <i>International Journal of Cancer</i> 48, issue 6 (1991): 816-820.	1.0 (0.8-1.3) if 1 IA; .9 (0.7-1.2) if > 2 IA	No	Null/Negative	Italy
22	1992	Fabio Parazzini, Carlo La Vecchia, Eva Negri, Silvia Franceschi, and Luca Boccione, "Menstrual and reproductive factors and breast cancer in women with family history of the disease," <i>International Journal of Cancer</i> 51, issue 5 (1992): 677-681.	1.0 (0.4-2.2)	No	Null	Italy
23	1993	A.E. Laing, F.M. Demenais, R. Williams, G. Kissling, V.W. Chen, and G.E. Bonney, "Breast Cancer Risk Factors in African-American Women: The Howard University Tumor Registry Experience," <i>Journal of the National Medical Association</i> 85 (1993): 931-939.	4.7 (2.6-8.4) if IA and diagnosed BC ≥ 50 yrs old; if BC 41-49 yrs old, 2.8 (1.0-8.1); if BC ≤ 40 yrs old, 1.5 (0.7-3.5)	Yes/Marginal /No	Positive	United States
24	1993	Carlo La Vecchia, Eva Negri, Silvia Franceschi, Fabio Parazzini, "Long-term impact of reproductive factors on cancer risk," <i>International Journal of Cancer</i> 53, issue 2 (1993): 215-219.	1.0 if 1 IA, ns; .8 if ≥ 2 IA, p < .05	No/Yes	Null/Negative	Italy
25	1993	Miriam Moseson, Karen L. Koenig, Roy E. Shore, and Bernard S. Pasternack, "The influence of medical conditions associated with hormones on the risk of breast cancer," <i>International Journal of Epidemiology</i> 22, issue 6 (1993): 1000-1009.	1.0 (0.7-1.4)	No	Negative	United States

26	1994	N. Andrieu, F. Clavel, B. Gairard, L. Piana, A. Bremond, J. Lansac, R. Flamant, and R. Renaud, "Familial risk of breast cancer and abortion," <i>Cancer Detection and Prevention</i> 18, no. 1 (1994): 51-55.	1.2 (0.8-1.8) if 1 IA; 9 (5-1.7) if ≥ 2 IA	No	Positive/Negative	France
27	1994	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," <i>Journal of the National Cancer Institute</i> 86 (1994): 1584-1592.	1.5 (1.2-1.9)	Yes	Positive	United States
28	1994	A.E. Laing, G.E. Bonney, L. Adams-Campbell, et al., "Reproductive and Lifestyle Risk Factors for Breast Cancer in African-American Women," <i>Genetic Epidemiology</i> 11 (1994): A300.	2.44 (1.0-6.0)*	Yes	Positive	United States
29	1995	N. Andrieu, S.W. Duffy, T.E. Rohan, M.G. Lè, E. Luporsi, M. Gerber, R. Renaud, D.G. Zaridze, Y. Lifanova, and N.E. Day, "Familial Risk, Abortion and Their Interactive Effect on the Risk of Breast Cancer—A Combined Analysis of Six Case-Control Studies," <i>British Journal of Cancer</i> 72, no. 3 (1995): 744-751.	1.5 (1.1-1.9) if 1 IA	Yes	Positive	Multinational
30	1995	Louise A. Brinton, Janet R. Daling Jr., Jonathan M. Liff, Janet B. Schoenberg, Kathleen E. Malone, Janet L. Stanford, Ralph J. Coates, Marilee D. Gammon, Louise Hanson, and Robert N. Hoover, "Oral contraceptives and breast cancer risk among younger women," <i>Journal of the National Cancer Institute</i> 87 (1995): 827-835.	0.98 (0.8-1.2) 1 IA; 1.02 (0.8-1.4) if ≥ 2 IA	No	Negative/Positive	United States
31	1995	L. Bu, L.F. Voigt, Z. Yu, K.E. Malone, and J.R. Daling, "Risk of breast cancer associated with induced abortion in a population at low risk of breast cancer," <i>American Journal of Epidemiology</i> 141 (1995): S85 (abstract 337).	2.9 (1.9-4.4) if 1 IA; 3.6 (2.2-6.0) if ≤ 2 IA; 4.5 (1.9-10.7) if BC ≤ 35 yrs old	Yes	Positive	China
32	1995	Loren Lipworth, Klea Katsouyanni, Anders Ekbohm, Karin B. Michels, and Dimitrios Trichopoulos, "Abortion and the Risk of Breast Cancer: A Case-Control Study in Greece," <i>International Journal of Cancer</i> 61 (1995): 181-184.	1.51 (1.24-1.84); 2.06 (1.45-2.9) if IA before FFTP among parous women	Yes	Positive	Greece
33	1996	Janet R. Daling, Louise A. Brinton, Lynda F. Voigt, Noel S. Weiss, Ralph J. Crates, Kathleen E. Malone, Janet B. Schoenberg, and Marilee Gammon, "Risk of Breast Cancer among White Women Following Induced Abortion," <i>American Journal of Epidemiology</i> 144 (1996): 373-380.	1.3 (1.0-1.6) if 1 IA	Marginal	Positive	United States
34	1996	Polly A. Newcomb, Barry E. Storer, Matthew P. Longnecker, Robert Mifftendorf, E. Robert Greenberg, and Walter C. Willett, "Pregnancy Termination in Relation to Risk of Breast Cancer," <i>Journal of the American Medical Association</i> 275 (1996): 283-287.	1.23 (1.0-1.51)	Marginal	Positive	United States

			Yes/Marginal	Positive	Netherlands
35	1996	Matti A. Rookus and Flora E. van Leeuwen, "Induced Abortion and Risk for Breast Cancer: Reporting (Recall) Bias in a Dutch Case-Control Study," <i>Journal of the National Cancer Institute</i> 88 (1996): 1759-1764.	1.9 (1.1-3.2); if before first birth, 2.6 (1.0-6.8)		
36	1996	R. Talamini, S. Franceschi, C. La Vecchia, E. Negri, L. Borsari, M. Montella, F. Falcini, E. Coni, and C. Rossi, "The Role of Reproductive and Menstrual Factors in Cancer of the Breast Before and After Menopause," <i>European Journal of Cancer</i> 32A, no. 2 (1996): 303-310.	1.2 (1.0-1.5) if 1 IA	Positive	Italy
37	1996	A. Tavani, C. La Vecchia, S. Franceschi, E. Negri, B. D'Avanzo, A. Decarli, "Abortion and breast cancer risk," <i>International Journal of Cancer</i> 65 (1996): 401-405.	1.2 (1.0-1.5)	Positive	Italy
38	1996	A.H. Wu, R.G. Ziegler, M.C. Pike, A.M. Nomura, D.W. West, L.N. Kolonel, P.L. Horn-Ross, J.F. Rosenthal, and R.N. Hoover, "Menstrual and reproductive factors and risk of breast cancer in Asian-Americans," <i>British Journal of Cancer</i> 73, no. 5 (1996): 680-686.	1.92 (0.7-5.3) if nulliparous and had only IAs	Positive	United States
39	1997	Mads Melbye, Jan Wohlfahrt, Jørgen H. Olsen, Morten Frisch, Tine Westergaard, Karin Helweg-Larsen, and Per Krøgh Andersen, "Induced Abortion and the Risk of Breast Cancer," <i>New England Journal of Medicine</i> 336, no. 2 (1997): 81-85.	1.00 (.94-1.06)	Null	Denmark
40	1997	Julie R. Palmer, Lynn Rosenberg, R. Sowmya Rao, Ann Zauber, Brian L. Strom, M. Ellen Warshauer, Paul D. Stolley, and Samuel Shapiro, "Induced and Spontaneous Abortion in Relation to Risk of Breast Cancer (United States)," <i>Cancer Causes and Control</i> 8 (1997): 841-849.	1.3 (9-1.9) if nulliparous; 1.1 (9-1.5) if parous; 1.4 (1.0-1.8) if (parous) IA after one birth	Positive	United States
41	1999	F. Fioretti, A. Tavani, C. Bosetti, C. La Vecchia, E. Negri, F. Barbone, R. Talamini, and S. Franceschi, "Risk factors for breast cancer in nulliparous women," <i>British Journal of Cancer</i> 78, no. 11/12 (1999): 1923-1928.	0.97 (0.64-1.47); if abortion \geq 30 yrs old, 1.75 (1.03-2.97)	Negative/Positive	Italy
42	1999	Pamela M. Marcus, Donna Day Baird, Robert C. Millikan, Patricia G. Moolman, Bahjat Qaqish, and Beth Newman, "Adolescent reproductive events and subsequent breast cancer risk," <i>American Journal of Public Health</i> 89, no. 8 (1999): 1244-1247.	1.2 (6-2.7) if first IA < age 20; 1.1 (.7-1.7) if first IA \geq age 20	Positive	United States
43	2000	DeAnn Lazovich, Julie A. Thompson, Pamela J. Mink, Thomas A. Sellers, and Kristin Anderson, "Induced abortion and breast cancer risk," <i>Epidemiology</i> 11, no. 1 (2000): 76-80.	1.1 (0.8-1.6); if IA nulliparous, 1.7 (0.6-5.4)	Positive	United States

44	2000	P.A. Newcomb and M.T. Mandelson, "A record-based evaluation of induced abortion and breast cancer risk," <i>Cancer Causes and Control</i> 11, no. 9 (2000): 777-781.	0.9 (0.5-1.6)	No	Negative	United States
45	2000	M.T. Tang, N.S. Weiss, K.E. Malone, "Induced abortion in relation to breast cancer among parous women: A birth certificate registry study," <i>Epidemiology</i> 11, no. 2 (2000): 177-180.	0.9 (0.7-1.2) if parous	No	Negative	United States
46	2001	M.J. Goidacre, L.M. Kurina, V. Seagroatt, and D. Yeates, "Abortion and Breast Cancer: A Case-Control Record Linkage Study," <i>Journal of Epidemiology and Community Health</i> 55, no. 5 (2001): 336-337.	0.83 (0.74-0.93) (observed v. expected BC cases)	Yes	Negative	Britain
47	2001	C. Robertson, M. Van Den Donk, M. Primic-Zakej, T. MacFarlane, and P. Boyle, "The association between induced and spontaneous abortion and risk of breast cancer in Slovenian women aged 25-54," <i>Breast</i> 10 (2001): 291-298.	2.71 (0.72-10.26) if IA nulliparous; 1.29 (.77-2.17) if uniparous	No	Positive	Slovenia
48	2001	M. Sanderson, X.O. Shu, F. Jin, Q. Dai, W. Wen, Y. Hua, Y.T. Gao, and W. Zheng, "Abortion history and breast cancer risk: Results from the Shanghai Breast Cancer Study," <i>International Journal of Cancer</i> 96, no. 6 (2001): 899-905.	1.0 (0.8-1.2) if premenopausal BC; .9 (.7-1.2) if postmenopausal BC	No	Null/Negative	China
49	2002	Z. Ye, D.L. Gao, Q. Qin, R.M. Ray, and D.B. Thomas, "Breast cancer in relation to induced abortions in a cohort of Chinese women," <i>British Journal of Cancer</i> 87, no. 9 (2002): 976.	1.06 (0.84-1.33)	No	Positive	China
50	2003	H. Becher, S. Schmidt, and J. Chang-Claude, "Reproductive factors and familial predisposition for breast cancer by age 50 years. A case-control-family study for assessing main effects and possible gene-environment interaction," <i>International Journal of Epidemiology</i> 32 (2003): 38-50.	1.35 (1.03-1.78)	Yes	Positive	Germany
51	2003	Gunnar Erlandsson, Scott M. Montgomery, Sven Cnattingius, and Anders Ekblom, "Abortions and breast cancer: record-based case-control study," <i>International Journal of Cancer</i> 103, no. 5 (2003): 676-679.	0.8 (0.64-1.0)	Marginal	Negative	Sweden
52	2003	M. Mahue-Giangreco, G. Ursin, J. Sullivan-Halley, and L. Bernstein, "Induced abortion, miscarriage, and breast cancer risk of young women," <i>Cancer Epidemiology, Biomarkers & Prevention</i> 12 (2003): 209-214.	1.05 (0.75-1.48) if parous, .40 or younger; .69 (.46-1.04) if nulliparous, .40 or younger	No	Positive/Negative	United States

			Yes	Negative	France
53	2003	Xavier Paoletti, Françoise Clavel-Chapelon, and the E3N group, "Induced and spontaneous abortion and breast cancer risk: results from the E3N cohort study," <i>International Journal of Cancer</i> 106, no. 2 (2003): 270-276.		0.91 (0.82-0.99)	
54	2004	Kathleen Meeske, Michael Press, Alpa Patel, and Leslie Bernstein, "Impact of reproductive factors and lactation on breast carcinomas in situ," <i>International Journal of Cancer</i> 110 (2004): 103-109.	No	1.04 (0.56-1.94) if nulliparous; .94 (.6-1.47) if parous, 1 IA	United States
55	2004	Julie R. Palmer, Lauren A. Wise, Lucile L. Adams-Campbell, and Lynn Rosenberg, "A prospective study of induced abortion and breast cancer in African-American women," <i>Cancer Causes & Control</i> 15, no. 2 (2004): 105-111.	No	1.1 (0.8-1.4) if parous; 0.9 (0.5-1.4) if nulliparous	United States
56	2005	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," <i>Journal of Epidemiology and Community Health</i> 59, no. 4 (2005): 283-287.	Yes	0.8 (0.72-0.89)	Scotland
57	2006	G.K. Reeves, et al., "Breast cancer risk in relation to abortion: Results from the EPIC study," <i>International Journal of Cancer</i> 119, no. 7 (2006): 1741-1745.	No	0.95 (0.87-1.03)	Europe
58	2006	K.A. Rosenblatt, D.L. Gao, R.M. Ray, M.R. Rowland, Z.C. Nelson, K.J. Wernli, W. Li, and D.B. Thomas, "Induced abortions and the risk of all cancers combined and site-specific cancers in Shanghai," <i>Cancer Causes and Control</i> 17, no. 10 (2006): 1275-1280.	No	1.01 (.92-1.12)	China
59	2006	Najmeh Tehrani, M. Ameibaraz, R. Saik, and S. Faghizadeh, "The effect of abortion on the risk of breast cancer" (Iranian study presented at a conference at McMaster University, 2006); http://hdl.handle.net/10755/163877	Yes	7.94 (2.05-26.21) with IA < 12 wks	Iran
60	2007	Karin B. Michels, Fei Xue, Graham A. Colditz, and Walter C. Willett, "Induced and Spontaneous Abortion and Incidence of Breast Cancer among Young Women," <i>Archives of Internal Medicine</i> 167, no. 8 (2007): 814-820.	No	1.01 (0.88-1.17)	United States
61	2007	Kourosh Holakouie Naieni, Ali Ardalani, Mahmood Mahmoodi, Abbas Motavalian, Yousef Yahyapour, and Bahareh Yazdizadeh, "Risk Factors of Breast Cancer in North of Iran: A Case-Control in Mazandaran Province," <i>Asian Pacific Journal of Cancer Prevention</i> 8, no. 3 (2007): 395-398. Available at http://www.apocp.org/cancer_download/Volume8_No3/395-398%20c_Naieni%204.pdf .	Yes	1.62 (1.13-2.31)	Iran

			No	Negative/ Positive	United States
62	2008	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," <i>Contraception</i> 77 (2008): 391-396.		.95 (.76-1.18) if nulliparous; 1.05 (0.92-1.2) if parous	United States
63	2008	Jie Lin and Jian-feng Yu, "A case control study on risk factors of breast cancer among women in Cixi," <i>Zhejiang Journal of Preventive Medicine</i> 20, no. 6 (June 2008): 3-5.	Yes	2.38 (1.09-5.2)	China
64	2009	Jessica M. Dolle, Janet R. Daling, Emily White, Louise A. Brinton, David R. Doody, Peggy L. Porter, and Kathleen E. Malone, "Risk Factors for Triple-Negative Breast Cancer in Women Under the Age of 45 Years," <i>Cancer Epidemiology, Biomarkers and Prevention</i> 18, no. 4 (2009): 1157-1166.	Yes	1.4 (1.1-1.8)	United States
65	2009	Vahit Ozmen, Beyza Ozcinar, Hasan Karanlik, Neslihan Cabioglu, Mustafa Tukenmez, Rian Disci, Tolga Ozmen, Abdullah Igci, Mahmut Muslimanoglu, Mustafa Kececi, and Atilla Soran, "Breast Cancer Risk Factors in Turkish Women—a University Hospital Based Nested Case Control Study," <i>World Journal of Surgical Oncology</i> 7, no. 37 (2009).	Yes	1.66 (1.39-1.98)	Turkey
66	2009	Peng Xing, Jiguang Li and Feng Jin, "A Case-Control Study of Reproductive Factors Associated with Subtypes of Breast Cancer in Northeast China," <i>Medical Oncology</i> 27, no. 3 (2009): 926-931.	Yes	1.26 (1.05-1.52) for luminal A breast cancer	China
67	2011	L. Khachatryan, R. Schampf, and S. Kagan, "Influence of diabetes mellitus type 2 and prolonged estrogen exposure on risk of breast cancer among women in Armenia," <i>Health Care for Women International</i> 32, no. 11 (2011): 953-971.	Yes	2.86 (1.02-8.04)	Armenia
68	2012	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," <i>Asian Pacific Journal of Cancer Prevention</i> 13 (2012): 33-35.	Yes	1.52 (1.21-1.92)	China
69	2012	Julie Lecarpentier, et al., "Variation in breast cancer risk associated with factors related to pregnancies according to truncating mutation location, in the French National BRCA1 and BRCA2 mutations carrier cohort (GENEPSO)," <i>Breast Cancer Research</i> 14, issue 4 (2012): R99.	No/Yes	(hazard ratio) 1.15 (.83-1.6) if 1 IA; 1.77 (1.19-2.63) if IA before FFTP	France

70	2013	Christina Marie Brauner, 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]. <i>Acta Obstetrica et Gynecologica Scandinavica</i> 92, issue 6 (2013): 700-705.	.95 (.83-1.09)	No	Negative	Denmark
71	2013	S. Jabeen, M. Haque, J. Islam, M.Z. Hossain, A. Begum, and M.A. Kashem, "Breast Cancer and Some Epidemiological Factors: A Hospital Based Study," <i>Journal of Dhaka Medical College</i> 22, no. 1 (2013): 61-66.	20.62	No	Positive	Bangladesh
72	2013	Ramchandra Kamath, Kamaleshwar S. Mahajan, Lena Ashok, T.S. Sanai, "A study on risk factors of breast cancer among patients attending the tertiary care hospital, in Udipi district," <i>Indian Journal of Community Medicine</i> 38, no. 2 (2013): 95-99.	6.38 (.99-40.81)	No	Positive	India

Meta-analyses

1	1996	Joel Brind, Vernon M. Chinchilli, Walter B. Severs, and Joan Summy-Long, "Induced Abortion as an Independent Risk Factor for Breast Cancer: A Comprehensive Review and Meta-Analysis," <i>Journal of Epidemiology and Community Health</i> 50, no. 5 (1996): 481-496.	1.3 (1.2-1.4)	Yes	Positive	(International)
2	2004	V. Berai, 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," <i>The Lancet</i> 363 (2004): 1 007-1016.	.93 (.89-.96)	Yes	Negative	(International)
3	2013	Yubei Huang, Xiaoliang Zhang, Weiqin Li, Fengju Song, Hongji Dai, Jing Wang, Ying Gao, Xueou Liu, Chuan Chen, Ye Yan, Yaogang Wang, and Kexin Chan, "A meta-analysis of the association between induced abortion and breast cancer risk among Chinese females," <i>Cancer Causes and Control</i> (2013): 1-10.	1.49 (1.23-1.74), ≥ 1 IA	Yes	Positive	China

KEY:

BC- Breast cancer
 IA- Induced abortion
 FFTP- First full-term pregnancy
 Luminal A cancer- Estrogen positive and HER2 negative
 Nulliparous- Has never given birth
 Parous- Has given birth
 *Odds ratio obtained from 1996 Brind

Appendix B: Sample mammography center form

Sample Breast History Form Mammography Center

Patient Label: Name, DOB, Age, MRN, Date

Personal Breast History

Have you ever had breast cancer?	N	Y	Right	Left	
If yes, what treatment did you undergo? (surgery- lumpectomy or mastectomy; radiation and/or chemotherapy)					
Have you been tested for the breast cancer gene (BRCA)?	N	Y	Are you BRCA positive?	N	Y
Do you have a lump that you can feel?	N	Y	Right	Left	
Do you have a lump that your doctor can feel?	N	Y	Right	Left	
Do you have a nipple discharge?	N	Y	Right	Left	
Do you have breast pain?	N	Y	Right	Left	
Is the breast pain new and in just one spot?	N	Y	Right	Left	
Have you ever had a previous breast biopsy?	N	Y	Right	Left	
When? _____	Results? _____				
Do you have breast implants or have had a breast reduction?	N	Y			
Have you ever had a breast cyst aspirated?	N	Y	Right	Left	
Have you ever had a previous mammogram?	N	Y	When? _____	Where? _____	
Have you ever had a breast ultrasound?	N	Y	When? _____	Where? _____	
Have you ever had previous breast MRI?	N	Y	When? _____	Where? _____	
Are you pregnant now?	N	Y	Date of Last Menstrual Period? ____/____/____		
Are you breastfeeding now?	N	Y	Have you breastfed in the last 6 months?	N	Y
Comments/Explanation _____					

Personal and Family Cancer History:

Are you of Ashkenazi Jewish descent (there is higher incidence of BRCA gene)? **N** **Y**

Have YOU or any of your family members ever been diagnosed with any of the following?

Breast Cancer	N	Y	What relation? _____	Mother or father's side? _____	Age at diagnosis _____	Present Age _____
Colon Cancer	N	Y	What relation? _____	Mother or father's side? _____	Age at diagnosis _____	Present Age _____
Ovarian Cancer	N	Y	What relation? _____	Mother or father's side? _____	Age at diagnosis _____	Present Age _____
Uterine Cancer	N	Y	What relation? _____	Mother or father's side? _____	Age at diagnosis _____	Present Age _____

Alcohol History: Do you drink alcohol? **N** **Y** How many drinks per week? _____

Tobacco History: Have you ever smoked? **N** **Y** Age started: _____ Age when quit _____ Packs per day: _____

Radiation History:

Have you ever received radiation (Xrays) exposure to your chest wall? (e.g., Hodgkin's therapy, repeated fluoroscopies) **N** **Y**

Sun Exposure History: Frequent sun exposure (past or present)? **N** **Y** Frequent sunburns? **N** **Y**

Hormonal Drug History:

Have you ever used a hormone replacement? (e.g., estrogen, progesterone, Provera, Premarin) **N** **Y**

Name: _____ Age when started: _____ Age when stopped: _____ How long used(yrs)? _____

Have you ever used fertility drugs? (e.g., Clomid, Pergonal) **N** **Y**

Did you or your mother ever use DES (Diethylstilbestrol)? **N** **Y**

Contraceptive History:

Have you ever used any of the following? Birth Control Pills? **N** **Y**

Name: _____ Age when started: _____ Age when stopped: _____ Reason for discontinuing? _____

Name: _____ Age when started: _____ Age when stopped: _____ Reason for discontinuing? _____

Contraceptive injectable and/or device? (e.g., Nueva Ring, Norplant, Depoprovera, Mirena IUD,IUD, Patch) **N** **Y**

Name: _____ Age when started: _____ Age When stopped: _____

Reproductive History: Do you have regular periods? **N** **Y** Age at first period _____ Age at menopause _____

Have you ever been pregnant? N Y If yes, have you ever had preeclampsia? N Y
 If yes, how many times? _____

If, yes, **Please fill in the chart below for each of your pregnancies:**

1) your AGE in years at the end of your pregnancy

2) length of each pregnancy in number of weeks(full-term pregnancy is 40 weeks,)

For example: if you had a baby full term, when you were 25 years old, you would put 25 next to "1) Your age" and 40 next to live birth
 if you had a miscarriage at 7 weeks, you would put a 7 in the miscarriage line;
 if you had twins at 34 weeks you would put 34 next to the multiple birth line

Pregnancy	1st	2nd	3rd	4th	5th	6th	7th
1) Your AGE @ end of pregnancy							
2) What was the outcome of each pregnancy?							
Live Birth: How many weeks?							
Multiple Birth: How many weeks?							
Still Birth: How many weeks?							
Miscarriage: How many weeks?							
D&C after fetus (baby) died: How many weeks?							
Abortion: How many weeks?							
Ectopic Pregnancy: How many weeks?							
3) Did you breastfeed? How many weeks?							

Personal Information:

Height: _____ Weight: _____ Race: _____

STOP

Mammography Technologist Information

- Baseline
- Annual Exam
- Diagnostic:
 - New Symptom
 - Short Term Follow Up Unilateral
 - Short Term Follow Up Bilateral
 - Outside Additional Views
 - History of Breast Cancer

Was patient told to get outside previous films?
 YES N/A

From Where? _____

Notes _____

On the diagram, draw in the following if applicable:
 Palpable Lumps- ▽ Moles- O Scars- †

Left _____ Right _____

Chief Complaint _____

Safety Precautions

- Adequate Shielding of patient
- Adequate Shielding of Technologist
- Operation of Equipment Safety
- Wearing of Monitoring Badge
- Protection of Electrical Hazard
- Infection Control Precautions Equipment
- SMC/JCAHO Hand Washing standards met

Technologists Initials _____

Patient Label:
 Name, DOB, Age, MRN, Date

Appendix C: Sample clinical office form

Last Name: _____ First Name: _____ Date: _____
 Date of Birth: _____ Race _____ Height: _____ Weight: _____

Breast History and Risk Assessment Form

(Please use black ink only)

Circle Yes or No where indicated

Personal Breast History:

Have you ever had a previous mammogram?	Yes / No	Year	Results
Have you ever had a previous ultrasound?	Yes / No	Year	Results
Have you ever had previous MRI?	Yes / No	Year	Results
Have you ever had a previous breast biopsy?	Yes / No	Right / Left	Year
Have you ever had a breast cyst aspirated?	Yes / No	Right / Left	Year
Do you have breast pain?	Yes / No	Right / Left	
Do you have a lump that you can feel?	Yes / No	Right / Left	
Do you have a lump that your doctor can feel?	Yes / No	Right / Left	
Do you have regular periods?	Yes / No	If "Yes" LMP Date: _____	
Do you have a nipple discharge?	Yes / No		
Are you BRCA positive?	Yes / No / Not Tested		

Family History:

Have YOU or any of your FAMILY members ever been diagnosed with any of the following?

	Yes/No	Relation to you?	Mother's Side or Father's Side	Age at Diagnosis	Present Age
Breast Cancer	Yes/No				
Colon Cancer	Yes/No				
Ovarian Cancer	Yes/No				
Uterine Cancer	Yes/No				

Radiation History:

Have you ever received radiation exposure to your chest wall? (e.g., Hodgkin's therapy, repeated fluoroscopies) Yes / No

Alcohol and Tobacco History:

Do you drink alcohol?	Yes / No	How much?			
Have you ever smoked?	Yes / No	Age Started	Age quit	Packs per day	

Sun Exposure History:

Frequent sun exposure (past or present)? Yes / No Frequent sunburns? Yes / No

(PLEASE TURN PAGE OVER AND COMPLETE BACK OF THIS FORM)

Last Name: _____ First Name: _____ Date: _____
 Date of Birth: _____ Race _____ Height: _____ Weight: _____

Reproductive History:

Age at first period _____ Age at Menopause _____

Have you ever been pregnant? **Yes / No** If "Yes", how many times? _____ Have you ever had pre-eclampsia? **Yes / No**

(If you have never been pregnant, skip to "Hormone / Contraceptive History section")

Please fill in the length of each pregnancy by the # of weeks: (a full term pregnancy is 40 weeks)

Pregnancy	1 st	2 nd	3 rd	4 th	5 th	6 th	7 th
How old were you at the end of each pregnancy?							
Live birth: How many weeks pregnant were you?							
Multiple births: How many weeks pregnant were you?							
Still births: How many weeks pregnant were you?							
Miscarriage: How many weeks pregnant were you?							
D&C after fetus (baby) died: How many weeks pregnant were you?							
Abortion: How many weeks pregnant were you?							
Ectopic pregnancy: How many weeks pregnant were you?							
Did you breast feed? If "yes", for how many weeks?							

Hormonal Drug History:

Have you ever use a hormone replacement? (Ex: estrogen, progesterone, Provera, Premarin) **Yes / No**

Name of drug _____ Age when started? _____ Age when stopped? _____

Have you ever used fertility drugs? (Ex: Clomid, Pergonal, etc.) **Yes / No**

Name of drug _____ Age when started? _____ Age when stopped? _____

Contraceptive History:

Have you ever used birth control pills? **Yes / No** If "Yes" please provide the following information

Name of drug	Age when started	Age when stopped	Reason for discontinuing

Have you ever used contraceptive injectable medications and / or devices (Ex: NuevaRing, Norplant, Depo-Provera, IUD, Patch)? **Yes / No**

If "Yes" please provide the following information:

Name of drug or device	Age when started	Age when stopped	Reason for discontinuing

Appendix D: Major points on induced abortion and breast cancer

Developmental biology and the results of epidemiologic and ecological epidemiological studies show that induced abortion is an **independent risk** factor for breast cancer. The existing studies fulfill the Bradford Hill Causality Guidelines, the same guidelines that were fulfilled to show cigarettes are a **cause** of lung cancer.

Breast lobule vulnerability

- Cells reproduce themselves through cell division, during which a complete new copy of all genes (DNA) is made.
- The more quickly cell division occurs, the more likely errors (mutations) are to be produced.
- Type 1 and Type 2 lobules are cancer-vulnerable, in part because their cells reproduce quickly, potentially leading to multiple mutations (e.g., genetic copying errors) and eventual cancer.
- Type 3 and Type 4 lobules are cancer-resistant, in part because their cells reproduce more slowly, during which time genetic errors can be repaired.
- Type 3 lobules form when milk production stops in Type 4 lobules.

Breast lobule development

- At birth, infants have cancer-vulnerable Type 1 lobules in their breasts.
- During puberty, cancer-vulnerable Type 2 lobules develop from some Type 1 lobules.
- By the end of puberty, females have 75 percent Type 1 lobules and 25 percent Type 2 lobules in their breasts, all cancer-vulnerable.
- During pregnancy, in preparation for breastfeeding, the number of Type 1 and Type 2 lobules in the breast increase in number as the breast **doubles** in volume during the first 20 weeks of pregnancy, **increasing** the number of places for cancers to start.
- At around week 20, Type 1 and Type 2 lobules commence maturation into Type 4 lobules, which produce which produce colostrum, the early milk.
- By week 32, sufficient Type 4 lobules have formed that a woman's breasts are resistant to cancer.
- At birth, by week 40, approximately 70 to 90 percent of Type 1 and Type 2 lobules have matured into Type 4 lobules.
- After a mother ceases to breastfeed (or if she does not breastfeed), Type 4 lobules become cancer-resistant Type 3 lobules, which possess the same epigenetic changes that afford Type 4 lobules cancer resistance.

Reproductive protections against breast cancer

- Early first full-term pregnancy (around age 20) is protective against breast cancer, because the period of time when the majority of the breast tissue is comprised of cancer-vulnerable Type 1 and 2 lobules (susceptibility window) is shortened.

- Breastfeeding diminishes breast cancer risk by maintaining maximum numbers of Type 4 lobules and decreasing the number of menstrual cycles and ovulations a woman experiences.
- For each year a woman delays her first full-term pregnancy after the age of 20, she increases her risk of premenopausal breast cancer by 5 percent per year and postmenopausal breast cancer 3 percent per year.
- Each pregnancy after her first reduces a woman's risk of breast cancer by 10 percent.

Reproductive factors that do not contribute to breast cancer

- First-trimester spontaneous abortions (that is, miscarriages) do not generally increase breast cancer risk, because they are normally caused by decreased hormonal levels that prevent cancer-vulnerable Type 1 and Type 2 lobules from proliferating in the first place.

Reproductive risks for breast cancer

- Nulliparity (childlessness)
- Later first full-term pregnancy increases risk of breast cancer.
- Second-trimester miscarriage increases breast cancer risk, because it is usually due to physical problems causing fetal death, rather than low hormonal states.
- Premature birth before 32 weeks increases breast cancer risk.
- Induced abortion increases breast cancer risk.
- Each induced abortion increases the risk of premature birth further, and premature birth before 32 weeks doubles breast cancer risk.
- Second-trimester miscarriages, births before 32 weeks, and induced abortions increase breast cancer risk, because cancer-vulnerable Type 1 and Type 2 lobules have proliferated in the breasts but do not mature in sufficient numbers into cancer-resistant Type 4 lobules, because the pregnancy will not continue to 32 weeks.

Breast cancer development

- Breast cancer takes at least eight to 10 years to grow into a detectable tumor, based upon what is known of cell doubling times. Thus, after an induced abortion, a resultant breast cancer may not be detectable for eight to 10 years.

Studies that affirm the abortion-breast cancer link

- At least 72 epidemiologic studies and three meta-analyses differentiating between induced and spontaneous abortion (or whose data have been reanalyzed to so differentiate) as a risk for breast cancer have been published since 1957; 21 studies and two meta-analyses show some positive, statistically significant association between induced abortion and breast cancer, and seven studies show a positive, marginally statistically significant association.

- At least two ecological epidemiological studies²⁰⁰ (Remmennick and Carroll) of the induced abortion-breast cancer link show a strong association between induced abortion and breast cancer.

Biases common in studies of the induced abortion-breast cancer link

- Incomplete questionnaires, low user response, and unsuitable circumstances for obtaining data: In one large study, over half of respondents did not completely answer the study's question on abortion history. The authors filled in the blank halves of their responses with "no." Another analysis used a large national survey to which the rejection rate was over 60 percent. Data obtained through interviews at home or over the telephone may be affected by reporting bias.
- Health bias or survivor bias: Many studies assessing women with breast cancer intentionally exclude women with *in situ* breast cancer or a previous history of breast cancer. The exclusion of women who have suffered (and perhaps died) from the disease of interest, whether invasive or *in situ* breast cancer, introduces health bias or survivor bias into the study, and it may artificially shrink the demonstrated effect of induced abortion on breast cancer risk.
- Incorrect time frames: It takes an average of eight to 10 years for a breast cancer cell to become clinically detectable. Many studies fail to account for this and do not follow women long enough after induced abortions or establish the right time frames for analyzing the relationship between induced abortion and breast cancer.
- Unsophisticated analysis: Some analyses only assess the effect of general induced abortion history on breast cancer risk. However, the circumstances of an induced abortion determine the extent of its influence on breast cancer risk: the number of abortions procured, parity status at the time of an induced abortion, the age at which a woman procures an abortion, and the gestational stage at which it occurs.
- Unsuitable comparisons: Choosing correct reference groups in analyses is essential for the effect of induced abortion to be clear. Aborting women and nulliparous women must be compared to parous women with no abortion history.
- Other problems may affect these studies, such as issues with reporting surrounding abortion law changes, omitted variable bias, incomplete reporting and distinguishing between spontaneous and induced abortions, publication bias, insufficient sample randomization, very small sample sizes, failure to distinguish between first- and second-trimester spontaneous abortions, and incompletely explained models.

Research recommendation. The already extensive NAPBC accredited and FDA-regulated mammogram screening centers network should be transformed to do prospective

²⁰⁰ Examine trends in large populations based upon government-maintained statistical records.

research. With minor, inexpensive modifications, this network will yield vast amounts of data on the myriad factors that can lead to breast cancer.

Appendix E: The nature of the induced abortion-breast cancer link and the interval between exposure and disease

A review of the shape of the plotlines is illustrative of the nature of induced abortion's relationship with breast cancer.²⁰¹

Figure 1, Daling²⁰²: Risk of developing breast cancer after an induced abortion compared to women with no induced abortion history, with respect to interval between first abortion and reference date

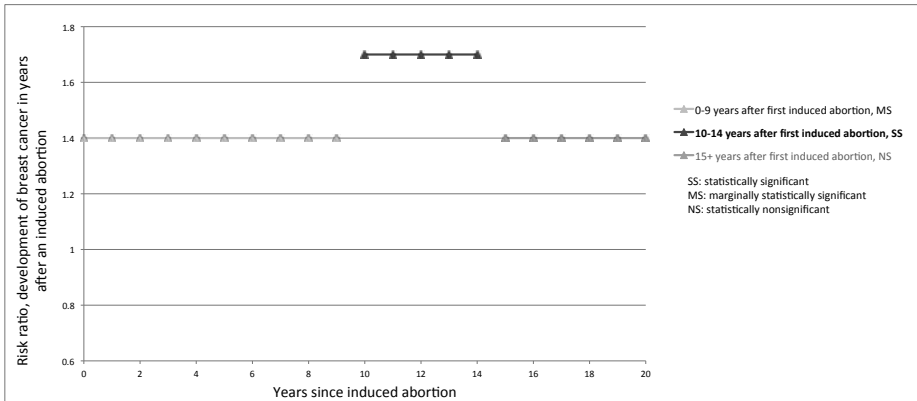
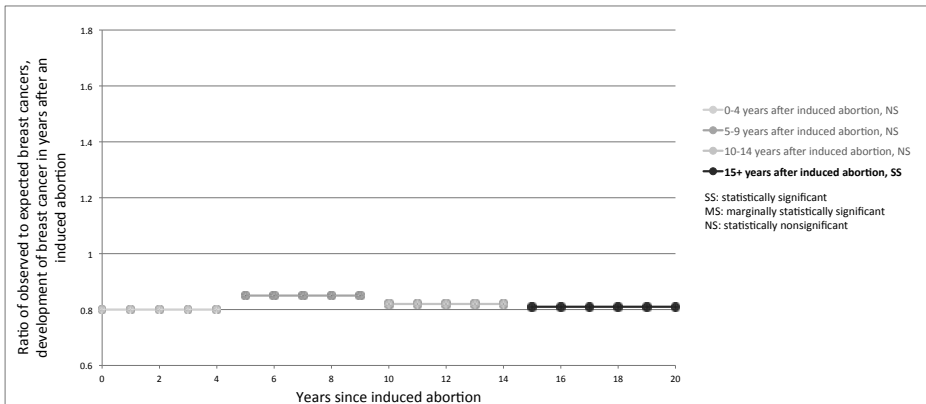


Figure 2, Goldacre²⁰³: Ratio, observed to expected breast cancers in sample population with respect to time interval between induced abortion and breast cancer

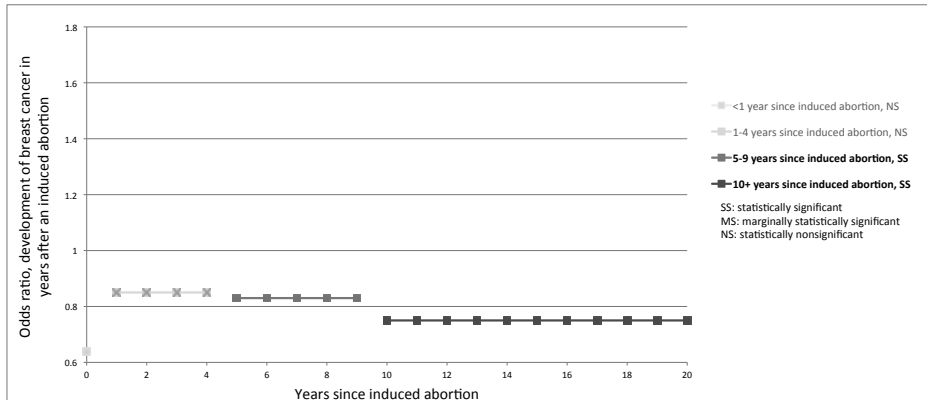


²⁰¹ Note that the varying significance levels in each plotline are different, but not the varying risk ratios (or odds ratios, or observed to expected ratios).

²⁰² 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.

²⁰³ 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.

Figure 3, Brewster²⁰⁴: Odds of developing breast cancer for women who have had a pregnancy ending in induced abortion compared to women with no pregnancy ending in induced abortion, with respect to years since induced abortion



The Daling study shows a positive, statistically significant influence on breast cancer risk for induced abortion between 10 and 14 years after it is procured. A positive and marginally statistically significant influence on breast cancer is detected in the first zero to nine years after an induced abortion is procured. No statistically significant influence is detected 15 or more years after an induced abortion is procured.

The Goldacre study does not show a statistically significant difference in observed and expected breast cancer rates among women with an induced abortion in the first four years, five to nine years, or 10 to 14 years after it is procured. Fifteen or more years after its procurement, induced abortion is shown to have a statistically significant and negative influence.

The Brewster study finds no statistically significant influence for induced abortion in under one year or in one to four years after its procurement. Five to nine years and 10 or more years after its procurement, induced abortion is shown to have a statistically significant and negative influence on breast cancer risk.

In short, the available data show induced abortion to have a positive, significant influence on breast cancer risk approximately 10 to 14 years after its procurement. In the first 10 years after an abortion is obtained and from about 15 years onward after it is obtained, induced abortion is not shown to have a positive, statistically significant influence on breast cancer risk. This “one-shot” increase in breast cancer risk seems to indicate that induced abortion is itself a carcinogenic experience and is not merely a weakening to a woman’s defenses against breast cancer. We operate under this assumption in our critiques of epidemiological studies of breast cancer and its potential risk factors.

²⁰⁴ 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.

These analyses and the figures they produced are not perfectly comparable. However, there is a paucity of data available on the development of breast cancer relative to the number of years past since an induced abortion: Daling, Goldacre, and Brewster's studies were the only three containing an analysis of this relationship.²⁰⁵

²⁰⁵ Daling et al. assess the risk of *in situ* and invasive breast cancer in gravid (i.e., have been pregnant) women with a history of induced abortion. Their model includes variables for number of induced abortions, age at first induced abortion, gestational length of first aborted pregnancy, timing of first induced abortion with respect to first birth (if any), interval between first abortion and reference date (i.e., time of diagnosis for breast cancer patients and "a comparable date for controls") and stage of disease at diagnosis. The risk ratios derived with this model are adjusted for "age, family history of breast cancer, religion, and age at first pregnancy."

Goldacre et al. compare the number of observed breast cancer cases in their sample to the number of breast cancer cases to be expected to develop in their sample. This analysis was stratified by age, "year of occurrence of case or control event" (i.e., year of breast cancer diagnosis, among cases, or year of other surgical or medical event, in controls), place of residence, and (incompletely) social class.

Brewster et al. assess the risk of breast cancer with induced abortion as compared to never-aborting women. Their model includes variables for induced abortion history, week of gestation of earliest abortion, age at abortion, number of abortions, time since abortion in years, and the timing of induced abortions with respect to parity status. The odds ratios derived from this model are adjusted for age and, in many cases, parity and age at first birth.