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# The breast cancer epidemic: 10 facts

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*Breast cancer, affecting one in eight American women, is a modern epidemic. The increasing frequency of breast cancer is widely recognized. However, the wealth of compelling epidemiological data on its prevention is generally not available, and as a consequence, is largely unknown to the public. The purpose of this report is to review the epidemiological evidence of preventable causes of breast cancer.*

*Keywords*: Breast cancer epidemic, Delayed childbearing, Breast cancer susceptibility window, Hormone replacement therapy, Oral contraceptives, Levonorgestrel, Induced abortion, Breast feeding

## Introduction

Affecting one in eight U.S. women, breast cancer is a modern American epidemic. This review contains 10 facts that summarize the emerging epidemiology of this tragic development. Table 1 contains the abbreviations and terms frequently used in this review. The incidence of breast cancer has risen dramatically during the last four decades (Facts 1–3). Moreover, a growing international acceptance of Western style sexual and reproductive practices has been associated with an increase in worldwide breast cancer rates. A number of breast cancer risk factors that are potentially preventable are now established. An early epidemiological insight was that a delay (or avoidance) of childbearing (Fact 4) raises the risk of breast cancer. Similarly, a reduced duration (or avoidance) of breastfeeding, is a loss of a natural breast cancer preventive (Fact 8).

A greater understanding of the cancer-protective physiological mechanisms that occur during the first full-term pregnancy (FFTP) has resulted in an enhanced understanding of the breast cancer "susceptibility window" that occurs between puberty and the FFTP (Fact 5).

Hormones, both in the form of combined hormone replacement therapy (CHRT, Fact 6) and combined oral contraceptives (COCs, Fact 7) increase the risk of breast cancer. The World Health Organization (WHO) has recognized CHRT as a Group 1 carcinogen. Likewise, the WHO has recognized COCs as Group 1 carcinogens for breast cancer, as well as for cervical and liver cancer. The


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***Table 1*** *Frequently used abbreviations and terms (listed alphabetically)*

| Abbreviations | Terms |
|---|---|
| ABC link | Abortion–breast cancer link |
| CEE(s) | Conjugated equine estrogen(s) |
| CHD | Coronary heart disease |
| CHRT | Combined hormone replacement therapy |
| CI | Confidence Interval |
| COC(s) | Combined oral contraceptive(s) |
| EC | Emergency contraception |
| ECP(s) | Emergency contraception pill(s) |
| ERT | Estrogen replacement therapy |
| FDA | Food and Drug Administration |
| FFTP | First full-term pregnancy |
| HRT | Hormone replacement therapy |
| IA(s) | Induced abortion(s) |
| IARC | International Agency for Research on Cancer |
| MPA | Medroxyprogesterone acetate |
| OC(s) | Oral contraceptive(s) |
| OR | Odds ratio |
| OTC | Over-the-counter |
| POC(s) | Progestin-only contraceptive(s) |
| RR | Relative Risk |
| WHI | Women's Health Initiative |
| WHO | World Health Organization |

carcinogenic risk of progestin-only contraceptives (POCs) is at least comparable to the risk of COCs.

Many reports from the United States and other Western countries have also linked induced abortion (IA) to breast cancer (the abortion–breast cancer (ABC) link, Fact 8). Recently, there has been a surge in the number of reports from multiple, non-Western nations, associating abortion with breast cancer (Fact 8). Consequently, there is now sufficient evidence to conclude that IA is causally linked to breast cancer (Fact 9).

There is also evidence of a compounding of breast cancer risk factors in girls and young women (Fact 10). Recent epidemiological research found a large increase in this malignancy in young women that is metastatic (to bone, brain, and lungs) at the time of diagnosis. This ominous development has "no recommended screening practice" and a dismal prognosis (Johnson, Chien, and Bleyer 2013). This sobering trend mandates the need for disclosure of breast cancer risk factors. A medical, legal, and ethical duty for full and accurate informed consent exists for all females. This is especially imperative for a girl (with her parent or guardian), or a young woman, who is considering the choice of an oral contraceptive (OC), including so-called "emergency contraception (EC)," IA (or both) during her "susceptibility window" (Fact 10).

Breast cancer is emerging as a more preventable disease than has been previously recognized. More than 40 years ago, physician, former head of Harvard

Epidemiology and pioneer breast cancer researcher, Brian MacMahon concluded, "One of the most important contributions of epidemiology to the fight against cancer has been the demonstration that many of the prevalent forms of human cancer are *preventable*" [Emphasis added] (MacMahon 1969). A growing, and predominantly international body of literature on breast cancer preventable risk factors, has affirmed his prescient words and is summarized in Fact 8.[1] The impressive reduction in the U.S. breast cancer rate, that followed the 2002 Food and Drug Administration (FDA) warning on hormone replacement therapy (HRT), has demonstrated the great potential impact that full and accurate informed consent has for breast cancer prevention (Facts 6 and 10).

## Fact 1: Breast Cancer Is Much More Common

There were an estimated 68,000 new cases of breast cancer among U.S. women in 1970 (Silverberg and Grant 1970). By 2014, there was a 242 percent increase (232,670) in new cases of female breast cancer (Siegel, Zou, and Jemal 2014). During this period—1970 to 2014—the U.S. population increased 56.8 percent (203,392,031 to 318,892,100). Thus, the rate of increase in female breast cancer has been more than 4-fold (i.e., 4.26-fold) the increase in the U.S. population during the same period.

By comparison, new cases of colon/rectal cancer in U.S. women rose 84.0 percent (39,000 to 71,760) between 1970 and 2014, surpassing the rise in the United States population during this same period by nearly half (1.48-fold) (Silverberg and Grant 1970; Siegel, Zou, and Jemal 2014). Even more astonishing, cigarette-related lung cancer in U.S. women rose 884 percent between 1970 and 2014 (11,000 to 108,210). Nonetheless, lung cancer still ranked a distant second to new cases of female breast cancer in 2014. The four most common new U.S. female cancers in 2014 are estimated by the American Cancer Society to be breast (232,670), lung/bronchus (108,210), colon/rectal (71,760), and uterine corpus (52,630) (Siegel, Zou, and Jemal 2014). Thus, breast cancer is expected to account for more new cancers in 2014 than the second, third, and fourth most common cancers combined.

## Fact 2: The Breast Cancer Epidemic Is a Relatively Recent Occurrence

There is now substantial evidence that there is an alarming increase in the incidence of breast cancer. Only four decades ago, there was much less concern regarding the rate of new cases.

The concern about breast cancer was at low ebb and had been so for approximately the first seventy years of the twentieth century. Breast cancer merited a mere two paragraphs in a 1973 American Cancer Society overview, as this update focused on other more noteworthy cancers (colon, rectum, lung, stomach, and pancreas) (Silverberg and Holleb 1973). The American Cancer Society reported in 1973, "In women less than 65 years of age," the breast cancer death rate has "shown little fluctuation" and is "almost unchanged since 1914" (Silverberg and Holleb 1973).

## Fact 3: The Breast Cancer Epidemic Is Ongoing

The increase in the incidence of breast cancer that began some 40+ years ago was abrupt. Moreover, this tragic epidemic continues, as evidenced by the annual

number of new cases of breast cancer in U.S. women at the beginning of each of the last five decades: 1970 (68,000), 1980 (110,000), 1990 (150,000), 2000 (182,800), and 2010 (207,090). This trend represents an alarming, even if slowing, rate of increase in the American breast cancer epidemic. Increases by decade have been: 1970s (+61.8%), 1980s (+36.4%), 1990s (+21.9%), and 2000s (+13.3%).

Breast cancer has clearly become much more common in the United States, and other developed Western countries, as well as developing nations (see Facts 8 and 9). The essential question is why?[2]

## Fact 4: The Role of Delayed Childbearing, Relative to Breast Cancer Risk, Was an Early Epidemiological Insight

Professor Brian MacMahon, MD (1923–2007), former head of the Department of Epidemiology at the Harvard School of Public Health, has been honored as the "founder of modern epidemiology" (Trichopoulos et al. 2008). He led a team of investigators, whose seminal Western work was published in 1970. After reviewing data from "seven areas of the world," this research team concluded that delayed childbirth increased the subsequent risk of breast cancer: "Women having their first child when aged under 18 years had only about one-third the breast cancer risk of those whose first birth is delayed until the age of 35 years or more" (MacMahon et al. 1970).

These same researchers subsequently confirmed that a delay in having a first baby did increase the risk of breast cancer. In fact, a woman's relative risk (RR) of breast cancer increased by 3.5 percent for every year of delay in age at first birth (Trichopoulos et al. 1983).

## Fact 5: There Is a Breast Cancer "Susceptibility Window" Before the First Full Term Pregnancy

Breast cancer surgeon, Angela Lanfranchi, MD, in collaboration with the Breast Cancer Prevention Institute, has contributed to a much greater understanding of normal breast development, as well as the pathophysiological mechanisms that lead to breast cancer.

A distinctive feature of the female breast is that this organ is not fully developed at birth. There is, of course, breast enlargement in girls at puberty, and this tissue is primarily stromal, or support tissue. However, between puberty and the FFTP, there is a "susceptibility window"—a time when the breast is "most susceptible to forming cancer" (Breast Cancer Prevention Institute 2007). This susceptibility occurs because the breast is composed primarily of Type 1 and Type 2 lobules.

Under the microscope, Type 1 and Type 2 lobules appear as twigs of a tree. Type 3 and Type 4 appear more like a cluster of grapes. Type 1 lobules account for 85 percent of all breast cancers, and Type 2 account for 12 percent of these cancers. Type 1 and Type 2 lobules have a higher density of hormone receptors, making them more susceptible to hormone stimulation that can result in cancer mutations.

During the FFTP, breast lobules mature and thereby develop a resistance to mutations that can result in cancer. Thus, differentiation follows "massive proliferation" (Ye et al. 2002). By the mid-second trimester of pregnancy, the breast contains "70 percent Type 4 cancer-resistant lobules and 30 percent immature cancer susceptible lobules" (Breast Cancer Prevention Institute 2007). Lanfranchi, further states, "by the end of the 3rd trimester, 85 percent of the breasts consists

of cancer-resistant Type 4 lobules containing colostrum" (Lanfranchi 2008). Human chorionic gonadotropin and human placental lactogen, both of which are made by the fetal-placental unit, cause significant maturation of breast tissue, as does prolactin (Lanfranchi 2008).

Thus, nature confers protection when a full-term pregnancy transforms the cancer susceptible breasts of puberty to the fully matured breasts containing the most resistant Type 4 lobules. Only 15 percent remain immature cancer susceptible lobules, "leaving fewer places for cancer to start" (Breast Cancer Prevention Institute 2007). Ironically, not only does the mother and her womb protect the baby, but the baby and his or her placenta protect the mother.

## Fact 6: Breast Cancer Occurrence Decreased Dramatically after Many U.S. Women Stopped Combined Hormone Replacement Therapy in 2002

The history of HRT is an ongoing and century-long story of efforts to treat menopausal symptoms including vasomotor instability. From the beginning of these efforts, however, there has also been a sub-text of preserving feminine youthfulness and attractiveness. This section summarizes the key historical points in the medical efforts to treat this condition, as well as the growth in the understanding of the associated risks. Menopause was first recognized in the medical literature in the late 1800s, but the twentieth century ushered in a "quest for treatment to maintain youthfulness, sexual health, and vitality" in women (Gast 2013). Unfortunately, the history of HRT includes grandiose claims, now disproved, and multiple, now substantiated harms to women, including breast cancer.

- Ovarian pig extracts (1910) promoted as a defense against aging—Czechoslovakian physician Arnold Lorand published his 1910 classic, "*Old Age Deferred*," and declared, "The years of the climacteric are the most troublesome in married life not only for the wife … but also in almost equal degree for the husband, who must show the greatest forbearance." Lorand claimed that extracts from pigs' ovaries could "put off old age for a score of years," or at least "mitigate its effects when it has asserted itself with all its terrors" (Cowley and Springen 2002).
- *Premarin* (1942)—The estrogen replacement hormone, Premarin, was patented and released in 1942 by Wyeth predecessor, Ayerst, after being extracted from, and named for PREgnant MAres' uRINe. The product is actually a mix of estrogenic compounds that are referred to as conjugated equine estrogens (CEEs).
- CEEs promoted for the prevention of coronary heart disease (CHD) (1960)—In 1960, the *New England Journal of Medicine* noted that, "It is now recognized that coronary-artery disease is increased in the postmenopausal state." Decreased ovarian function, whether in "postmenopausal" or "prematurely castrated women," "appears to be a rational basis for estrogen replacement therapy [ERT]." This study was undertaken "to determine the daily dosage of estrogen required to attain optimal lipid changes with minimal disturbing side effects." It concluded that, "a therapeutic trial of 2.5 mg [CEEs] is suggested in women with abnormal serum lipids previously subjected to hysterectomy. If the lipid abnormalities persist 5 or 10 mg daily should be tried." This amounted to a near universal endorsement of ERT for postmenopausal women, whether surgically induced or not, at a CEE dosage that was four to sixteen fold the

dose that would be used in the Women's Health Initiative (WHI). Relative to side effects, the authors noted nothing more serious than "transient breast tenderness" (Higano, Robinson, and Cohen 1960).

- Dr. Robert A. Wilson claimed HRT reduced the risk of breast and genital cancer (1962)—In 1962, Manhattan gynecologist, Robert A. Wilson concluded in a scientific *JAMA* report (not editorial) that taking "estrogens and progestins" reduced the risk of breast and genital cancers ("prophylactic effect"). This scientific report began with the expansive opening line, "There is no convincing proof that estrogen has ever induced cancer in the human being" (Wilson 1962).

  There was a noteworthy subtlety on the first page of Wilson's paper. Although, his study was of "estrogen and progestins" (medroxyprogesterone acetate, MPA, Provera), the report title was, "The roles of estrogen and progesterone in breast and genital cancer" (Wilson 1962). The implication was that the term, progesterone (the essential hormone of pregnancy) can be used interchangeably with a synthetic agent, a progestin.

  An authoritative review (2005) of progestins succinctly noted, "Progestins have been used for contraception for more than 30 years" (Erkkola and Britt-Marie 2005). In contrast, a meta-analysis of agents for luteal phase support due to iatrogenic infertility, found progesterone to be effective, but no synthetic progestin was found in this review to be effective as a fertility supplement (Pritts and Atwood 2002). The interchangeable use by Wilson of *progesterone* and *progestin*, implies a class of agents that would be assumed to have similar effects, or at least not opposite actions. The actions, however, relative to fertility are opposite, and as will be further discussed at the end of this section (Fact 6), there is also evidence against a "class effect" relative to the risk of breast cancer.
- Robert A. Wilson (*Feminine Forever*, 1966)—Wilson, published *Feminine Forever* four years later (1966). The observations and claims were not nuanced. He referred to menopausal women as "castrates," menopause as "living decay" and a "hormone deficiency disease, [that is] curable and totally preventable" (Wilson 1966). He further opined that with hormones "you find a woman 50 looking like 30," and that "every woman, no matter what her age, can safely live a fully sexed life for her entire life." HRT was not to be short-term therapy.

  *Newsweek* has called *Feminine Forever*, a "60s ode to estrogen" (Cowley and Springen 2002). Wyeth ran ads in medical journals urging physicians, "Treat her with Premarin. Keep her on Premarin."[3] What was not disclosed was that Wyeth reportedly paid Wilson to write his book, for consulting fees, for lectures to women's groups, and for thousands of copies of his book.[3]
- CEEs increase risk of endometrial cancer (1975)—In 1975, the *New England Journal of Medicine* published the results from a controlled trial. The risk-ratio for women on CEEs was 5.6 for those exposed for 1–4.9 years, and 13.9 for seven or more years of CEE usage. Thus, unopposed estrogen (Premarin only) use was found to increase the risk of endometrial cancer 5.6- to nearly 14-fold (Ziel and Finkle 1975). Following the release of this study, and the FDA-mandated warning letter from Wyeth in 1976, estrogen-only usage was limited to women who had undergone a hysterectomy.
- The addition of a *progestin (MPA)* to estrogens lowers risk of endometrial cancer (1980)—Gambrell et al., reported a four-year follow-up study (1980) of 10,872 women-years. The rate of

endometrial cancer was highest in the women on estrogens alone (359 per 100,000 women), intermediate in the untreated women (248/100,000 women), but lowest in women on a combination of estrogen-progestin (56/100,000 women, $P < 0.05$). Thus, the addition of a progestin significantly lowered the risk of endometrial cancer.

With the addition of a progestin to the CEEs, the use of Premarin once again increased. ERT transitioned to HRT. In the mid-1980s, the risk of osteoporosis was publicized, as well as its recommended treatment, HRT (Gambrell et al. 1980).

- The non-controlled *Nurses' Health Study* (1985)—This report showed that nurses who took hormones had less CHD than the general population. The NHS study was not controlled and did not settle the question of whether it was healthier women who took hormones, or whether hormones made women healthier (Stampfer et al. 1985).
- *The Heart and Estrogen/progestin Replacement Study* (HERS) Research Group controlled trial (1998), conjugated estrogens plus progestin (Prempro, 0.625 mg CEEs plus 2.5 mg of the progestin, MPA)—HERS was the first randomized controlled trial to examine the role of CHRT in the secondary prevention of CHD. The primary finding was "no overall cardiovascular benefit" (Hulley et al. 1998).
- The widely publicized WHI showed an increase in invasive breast cancer and cardiovascular disease (2002)—WHI was a controlled trial of CHRT versus placebo (Rossouw et al. 2002).[4] The study participants were 16,008 postmenopausal women between the ages of 50 and 79 years at initial screening. Slightly more than half (8,506) were given daily 0.625 mg of CEEs plus 2.5 mg of the progestin, MPA (Provera), in the form of Prempro 0.625/2.5 (Wyeth-Ayerst, Philadelphia, PA, released in 1996 for CHRT); the control group was given an identical appearing placebo.

The trial was stopped prematurely on May 31, 2002 "based on health risks that exceeded health benefits over an average follow-up of 5.2 years." There was an excess occurrence of "invasive breast cancer" that exceeded the "stopping boundary for this adverse effect[,] and the global index statistic" also supported the decision for a premature trial stoppage of this trial that was to have lasted 8.5 years (Rossouw et al. 2002).

The WHI study showed a 41 percent increase risk of stroke, 29 percent increase in heart attacks, 113 percent increase risk of pulmonary emboli, and a 26 percent increase in invasive breast cancer. Colorectal cancer was down 37 percent and hip fractures were 33 percent less common. Rather than the expected 40–50 percent reduction in coronary disease, "there was a 22 percent increase in total cardiovascular disease" despite improved lipid profiles (Rossouw et al. 2002).

The WHI results were big news and were rapidly broadcast by the secular media to the public. News magazines provided front-cover stories such as *Newsweek's*, "The end of the age of estrogen," which was standard fare (Cowley and Springen 2002). As a result of this information, almost half of the U. S. women, who had been taking HRT, quit their menopausal hormones. Sixty years after the release of Premarin, the number of HRT prescriptions dropped from 22 million per quarter to 12.7 million in the last quarter of 2003 (Cowley and Springen 2002). Promotion of HRT by the pharmaceutical industry declined as well. *Journal of the American Medical Association* reported that first quarter 2003 spending on standard-dose

Prempro, "the agent implicated by the WHI" report, was down 61 percent (Majumdar, Almasi, and Stafford 2004).[5]

Surprisingly, by late 2006, it was reported that there had been a 7 percent drop in the U.S. 2003 breast cancer rate. This drop occurred within only one year of women quitting their hormones, and amounted to a 12 percent drop (about 24,600 fewer cases—the equivalent of a small U.S. city being spared) among postmenopausal women who were estrogen-receptor positive. An M.D. Anderson Cancer Center statistician, Donald Berry, exclaimed, "When I saw it, I couldn't believe it" (Marchione 2006).

The deceleration in the rate of breast cancer rise in the 2000s may have been related, at least in part, to the continued reluctance by women to take these hormones.

- A University of California at San Francisco (UCSF) study (2010) found no evidence that the decline in breast cancer was tied a to change in mammogram screening—A UCSF, National Cancer Institute study of more than 2 million mammogram screenings performed on nearly 700,000 U.S. women also affirmed a breast cancer decline for both invasive breast and ductal carcinoma *in situ* cancers. This was the first time a study showed a direct link between reduced hormone therapy and declines in breast cancer. This drop in U.S. breast cancer was observed in women in their 50s and 60s, but not in premenopausal women in their 40s, who would not have stopped HRT (as they were not yet candidates for menopausal therapy). These researchers further noted that as "our analyses were adjusted for time between screening examinations, the effect of changes in mammography use is unlikely to explain our findings" (Farhat et al. 2010).

  These researchers suggested that hormones helped promote breast tumor growth of preexisting, clinically latent hormone-dependent cancers, not only increasing the incidence of invasive cancer, but also the risk of ductal carcinoma *in situ* (DCIS). The rapid decline between 2002 and 2003 in the incidence of breast cancer has been attributed to a loss of a HRT promoter ("fuel") effect, as opposed to an initiator role. The increased risk of breast cancer resolved rapidly after HRT cessation (Farhat et al. 2010). The decline in the rate of new cases of breast cancer persisted until 2006.
- An HRT review was published a month after the landmark WHI report, and its focus was estrogens (2002)—Although this review contained combined estrogens plus progestin data from HERS, WHI, and other reports, data were lumped into HRT users and nonusers (Nelson et al. 2002). No distinction was made between estrogen exclusive (ERT) versus combined estrogen plus progestin (CHRT) treatment. Noted HRT benefits were a decrease in colorectal cancer and osteoporotic fractures, and "Harms include[d] CHD, stroke, thromboembolic events, breast cancer with 5 or more years of use, and cholecystitis" (Nelson et al. 2002).

  Strangely, and without mention of concomitant progestin usage, was a sentence in the abstract's conclusions that read, "Current estrogen users have an increased risk of breast cancer that increases with duration of use" (Nelson et al. 2002). WHI did not report estrogen only (CEEs alone) data for prior hysterectomized women until 2011. Nonetheless, the focus in 2002 was on estrogen risk in the professional as well as the public media. This conclusion was

not evidence based, as the data reviewed was primarily from CHRT reports.

- The *Women's Health Initiative Memory Study (WHIMS)* showed more bad news for HRT (2003)—The WHIMS branch of the WHI study revealed that not only did CHRT not improve memory as had been proclaimed by R. A. Wilson four decades earlier (Wilson 1966), nor prevent cognitive deterioration (i.e., "mild cognitive impairment"), but it actually increased the risk of "probable dementia," among women ≥65 years (Shumaker et al. 2003).
- WHI also showed more abnormal mammograms and breast cancers diagnosed at an advanced stage (2003)—WHI researchers also reported, "Relatively short-term combined estrogen plus progestin use increases incident breast cancers, which are diagnosed at a more advanced stage compared with placebo use, and also substantially increases the percentage of women with abnormal mammograms. These results suggest estrogen plus progestin may stimulate breast cancer growth and hinder breast cancer diagnosis" (Chlebowski et al. 2003).
- A case–control study showing no increase in breast cancer with exclusive ERT of 25 years or longer (2003)—Essentially overlooked in the outpouring of reports from the WHI controlled trial, was a Puget Sound report that showed "no increase in breast cancer" or a "possible small effect" with 25 years or longer of exclusive ERT (Li et al. 2003). The use of combined estrogen and progestin (CHRT) was associated with a moderate increase in breast cancer risk. CHRT increased the risk of invasive ductal carcinoma, 2.6- to 3.7-fold, depending on duration of usage. CHRT increased the risk, even when ERT had also been used (Li et al. 2003).
- The *WHI quality of life study* did not find that women on HRT were healthier and happier (2003)—Despite the 1960s grand claims by Dr. Wilson (Wilson 1962, 1966), the *New England Journal of Medicine* reported, "Randomization to estrogen plus progestin resulted in no significant effects on general health, vitality, mental health, depressive symptoms, or sexual satisfaction" (Hays et al. 2003).
- *WHI* also found an *increased risk of ovarian cancer* (2003)—In 1962, Wilson had claimed that estrogens would reduce the risk of genital cancer. The WHI, however, found that the 2003 "randomized trial suggests that continuous combined estrogen plus progestin therapy [CHRT] may increase the risk of ovarian cancer while producing endometrial cancer rates similar to placebo" (CEEs alone). "The increased burden of endometrial biopsies required to assess vaginal bleeding further limits the acceptability of this regimen" (33% vs. 6%; $P < 0.001$) (Anderson et al. 2003). Endometrial cancer had long been recognized to be associated with estrogen only (CEEs) therapy (Ziel and Finkle 1975).
- *The 2010 WHI update* showed that CHRT resulted in both *a greater incidence of breast cancer and a higher breast cancer mortality* (2010)—This update showed that breast cancer was 25 percent more common in the CHRT (estrogen-plus-progestin, Prempro) group than the placebo group. Additionally, the cancers in the HRT group were more likely to be node positive, and there was a near doubling of breast cancer mortality (hazard ratio (HR), 1.96; 95 percent confidence interval (CI), 1.00–4.04; $P = 0.049$) (Chlebowski et al. 2010).
- *In 2011, WHI* reported that, when compared to placebo, *CEE-only treated women, with a history of prior hysterectomy, had a lower risk of breast cancer*

(2011)—The WHI Estrogen Alone Trial was "stopped after a mean of 7.1 years of follow-up because of an increased risk of stroke and little likelihood of altering the balance of risk to benefit by the planned trial termination date." The 2011 report was a "post-intervention" report of "postmenopausal women with prior hysterectomy followed up for 10.7 years, CEE use for a median of 5.9 years was not associated with an increased or decreased risk of CHD, deep vein thrombosis, stroke, hip fracture, colorectal cancer, or total mortality" (LaCroix et al. 2011). A decreased risk of breast cancer persisted (HR, 0.77; 95% CI, 0.62–0.95*)*. Thus, the risk of breast cancer was 23 percent lower in the CEE-only group.

- In 2012, the WHI reported CEEs alone did not have a role in breast cancer prevention (2012)—The WHI researchers provided the results from "subgroup analyses" of women with either benign breast disease or a family history of breast cancer. In neither group was there evidence of a reduction in breast cancer risk when CEEs were taken. Their conclusion was, "our data do not support use of oestrogen for breast cancer risk reduction because any noted benefit probably does not apply to populations at increased risk of such cancer" (Anderson et al. 2012). The major WHI findings are summarized in Tables 2–4.
- *Prempro legal fallout* (2013)—In late summer of 2013, the secular media reported, "Pfizer Inc. must pay about $1.8 million in punitive damages to a Connecticut woman who developed breast cancer after taking the company's Prempro menopause drug, a judge concluded." A jury in New Haven had previously awarded Margaret Fraser and her husband $4 million in compensatory damages in April 2012 after finding the world's largest drug-maker liable for her injuries. Thus, the total award was $5.76 million. The report further noted that, "The company has settled about 95 percent of the more than 10,000 lawsuits filed over the medicines and set aside about $1.6 billion to cover those accords —" (Feeley 2013).
- *Current Physicians' Desk Reference* (*PDR* 2013) *warning* and National Cancer Institute (NCI) statement—In 2013, the Premarin "boxed warning" stated, "Increased risks of myocardial infarction, stroke, invasive breast cancer, pulmonary embolism (PE), and deep vein thrombosis in postmenopausal women (50–79 yrs) reported," as well as "probable dementia in postmenopausal women ≥65 yrs reported" (Wyeth Pharmaceuticals, Inc. 2013). In fact, these are the WHI risks for combined CEE plus progestin (MPA, 2.5 mg), the ingredients of Prempro 0.625 mg/2.5 mg, rather than the risk of estrogen alone (Premarin). The NCI states that combined estrogen/progestin HRT (CHRT) is associated with "[a]pproximately a 26% increase in incidence of invasive breast cancer" (National Cancer Institute 2013). This statement is more precise and is WHI evidence based.

Thus, the focus of concern has shifted from the estrogens in CHRT being the source of the harms (Cowley and Springen 2002; Nelson et al. 2002) to questioning whether estrogens could have role in breast cancer prevention. Again, the WHI researchers have rejected this proposed strategy of CEEs alone for breast cancer prevention in women with a history of hysterectomy (Anderson et al. 2012). The progestins have increasingly become the primary focus of the harms**.** An additional concern is the interaction between the two, as has been implicated with the

***Table 2*** *Reported hazards of combined hormone replacement therapy (CHRT) by the Women's Health Initiative*

| **Hazards of CHRT** | **% Increase** |
|---|---|
| Invasive breast cancer (Rossouw et al. 2002; Manson et al. 2013) | +26, +28 |
| Increase in total cardiovascular mortality (Rossouw et al. 2002) (despite improved lipid profiles) | +22 |
| Increase in "heart attacks" (Rossouw et al. 2002) | +29 |
| Pulmonary emboli (Shumaker et al. 2003) | +113 |
| Probable dementia for women >65 yrs old (Shumaker et al. 2003) | +105 |
| Abnormal mammograms (Chlebowski et al. 2003) | +74 |
| Ovarian cancer (Anderson et al. 2003) | +58 |
| Breast cancer mortality (near doubling) (Chlebowski et al. 2003) | +96 |
| Stroke occurrence (Rossouw et al. 2002) | +41 |

fourth generation progestin in the OC YAZ.[6]

Evidence of just how far the pendulum has swung is demonstrated by a provocative 2013 article by Sturdee, "Are progestins really necessary as part of a combined HRT regimen?" (Sturdee 2013) Sturdee does not question the unacceptable risk of endometrial cancer with ERT in women with an intact uterus, or the amelioration of this risk that the addition of a progestin, such as Provera provides. Nor does he dispute the WHI findings of multiple harms from CHRTs with (CEEs plus Provera, CHRT), including, invasive breast cancer**,** cardiovascular disease, dementia, deep vein thromboses and pulmonary embolism (Sturdee 2013).

In a real sense, the heart of the problem was the confusion in terminology that was present, but not addressed by Wilson in his *Journal of the American Medical Association* report more than fifty years ago. He studied a *progestin*, but referred in the paper's title to "progesterone" (Wilson 1962). Can it be assumed that both exhibit a progestin "class effect?" (Sturdee 2013).

In 1967, a review by Wyeth Laboratories of the biological classification of progestational agents found that not only was there a "spectrum of activities" with each agent, but there was difficulty in classification (Edgren, Jones, and Peterson 1967).[7] This review quotes Maxwell Roland, "The area of endocrinology concerned with progestational steroids is

***Table 3*** *Anticipated benefits of combined hormone replacement therapy (CHRT) disproved by the Women's Health Initiative*

| **Disproved benefits of CHRT** |
|---|
| 40–50% reduction in coronary heart disease (Rossouw et al. 2002) |
| Improved general health (Hays et al. 2003) |
| Vitality (Hays et al. 2003) |
| Improved mental health (Hays et al. 2003) |
| Fewer symptoms of depression (Hays et al. 2003) |
| Sexual satisfaction (Hays et al. 2003) |
| Reduction in breast and genital cancer(Wilson 1962; Rossouw et al. 2002) |
| Prevent cognitive deterioration (Shumaker et al. 2003) |

***Table 4*** *Reported benefits of combined hormone replacement therapy (CHRT) by the Women's Health Initiative*

| **Benefits of CHRT*** | **% Reduction** |
|---|---|
| Lower incidence of colorectal cancer (Rossouw et al. 2002) | –37 |
| Fewer hip fracture (Rossouw et al. 2002) | –33 |

**Endometrial cancer rate reduced by 77 percent in non-WHI report (Gambrell et al. 1980).*

replete with controversy. Even the concept of progestogens is not free from ambiguity" (Rowland 1965).

The ambiguity (indistinctness or overlap in classification) in the terms *progesterone and progestin* is at base definitional. The term *progestin* is defined by *Stedman's* as (1) "a hormone of the corpus luteum, or (2) "a generic term for any substance, natural or synthetic, which effects some or all of the biological changes produced by progesterone" (*Stedman's medical dictionary* 2006). Likewise, the term-*classification* is defined by *Stedman's* as, "A systematic arrangement in classes or groups based on perceived common characteristics."

Bengiano et al. do not concur with the Stedman's classification and state, "The term progestogen has been widely utilized to indicate the general class of agents that include both progesterone and its synthetic analogs, whereas progestin refers only to synthetic progestational agents" (Bengiano, Primiero, and Farris 2004).

As previously noted (Fact 6), the *progestins* have been primarily used as OCs for more than five decades (Erkkola and Britt-Marie 2005). The pregnancy essential hormone, progesterone is, however, frequently also classified as a progestin. Stedman's refers to progestins as sharing "some or all of the biological" properties of progesterone (*Stedman's medical dictionary* 2006).[8] In fact, the effects of progesterone are opposite those of the synthetic progestins in clinically important areas**:** Synthetic progestins are anti-fertility agents (e.g., POCs including Plan B), whereas progesterone is used as luteal supplementation to treat infertility (Pritts and Atwood 2002; Erkkola and Britt-Marie 2005). The root of the term, *progestin*, is "progestation and -in." or pro-gestational—literally pregnancy promoting. Progestins, however, are primarily used to reduce (or eliminate) pregnancy.

Incisively, Sturdee notes, "the suggestion from the WHI that the effects of estrogen and progestins are a 'class effect' are clearly inaccurate, as there is particular evidence from the French E3N cohort studies of differential effects of progestins, with progesterone and dydrogesterone additions showing no increase in risk of breast cancer" (Sturdee 2013). The assumption that OC progestin, levonorgestrel, enhances fertility when used as EC (Plan B), through a class effect is likewise false.[9]

Similarly, the *Practice Committee of the American Society for Reproductive Medicine* has reviewed progesterone supplementation for the treatment of infertility. Although "early maternal progestogen exposure" has been linked to a risk of hypospadias, the Practice Committee concluded that progesterone supplementation poses no significant risk for any type of "birth defect" (Am Soc Reproductive Med 2008). Additionally, the manufacturer lists no increased risk of breast cancer with progesterone supplementation (Watson Laboratories, Inc. 2013).

The Practice Committee further states, "The FDA concluded that class labeling

for all progestogens [i.e., progestins] warning of an increased risk of birth defects was inappropriate because it would apply without regard to the indication for which the drug is prescribed." The FDA recognized this to be incoherent. Thus, progesterone is essentially opposite in clinical action to the synthetic progestins relative to fertility, birth defects and breast cancer risk.

The fifty-year history of lumping (or classifying) progesterone with the synthetic progestins, based on classic laboratory studies in the rat,[7,8] as if there is a "class effect" or "perceived common characteristics," has no more (human) clinical merit than assuming that the two components (CEEs and the progestin) of Prempro have the same risks, including breast cancer.

In late 2013, *Journal of the American Medical Association* published an integrated overview of the WHI findings. The overall finding from the intervention and poststopping phases of WHI was a 28 percent increased risk (95% CI, 1.11–1.48) of invasive breast cancer in women given CHRT, but a 21 percent reduced risk (HR 0.79, 95% CI, 0.61–1.02) of invasive breast cancer in women given CEEs only. This is additional evidence that the progestin component of the CHRT is the major source of the invasive breast cancer risk. The WHI researchers concluded, "Thus, the breast cancer findings were divergent between the two trials … [R]esults tended to be more adverse for CEE plus MPA [Prempro] than for CEE alone" (Manson et al. 2013).

In conclusion, CHRT (CEEs plus progestin, Prempro) poses multiple and substantial risks, including breast cancer. A decade ago, the focus was on the estrogen risk, but increasingly, the concern is with non-progesterone progestins, that are contained in CHRT, OCs and so-called EC (i.e., Plan B). An accompanying *Journal of the American Medical Association* editorial to the WHI overview concluded that "The Women's Health Initiative—[is] A Victory for Women." This editorial begins, "The history of medicine abounds with dogmas assumed and later overcome. Nowhere is that dynamic more evident than women's health. Several decades ago, menopausal hormones were widely assumed to be beneficial" (Nabel 2013). The grandiose claims of Wilson more than 50 years ago (Wilson 1962), regarding the benefits of CHRT, have been disproved. The women who stopped CHRT in 2002 chose wisely.

## Fact 7: Oral Contraceptives Are an Established Risk Factor for Breast Cancer

Evidence for an estrogen–breast cancer link was published in a *New England Journal of Medicine* review, "Estrogen Carcinogenesis in Breast Cancer" (Yager and Davidson 2006). Estrogen levels are 10–50 times higher in breast tissue than in blood, and are higher yet in cancerous tissue than normal tissue. Yager and Davidson stated that, "The strongest evidence for the role of estrogen in breast cancer has emerged from the experience" with the anti-estrogenic chemotherapy drug, tamoxifen, which has been shown to reduce the risk of cancer by 38 percent in the cancer-free breast (Yager and Davidson 2006).

OCs are known to accelerate cell division in girls and young women who take them before their FFTP. A *Mayo Clinic Proceedings* meta-analysis by Kahlenborn et al. demonstrated a 52 percent increase in the risk of premenopausal breast cancer among parous women who used OCs four or more years before their FFTP (odds ratio, OR, 1.52, 95% CI, 1.26–1.82) (Kahlenborn et al. 2006). In an

accompanying editorial Cerhan noted, "that a higher risk of breast cancer for OC use before first full-term pregnancy was first described more than 25 years ago" (Cerhan 2006). In other words, this overview finding by Kahlenborn et al. was not an outlier, but reflected a long-standing, even if seldom discussed, scientific understanding.

What was the media's response to this study with its troubling finding linking OCs and breast cancer? According to Dennis Byrne of the *Chicago Tribune,* their main response has been silence (Byrne 2007).

Potential media bias not withstanding, the OC is an established risk factor for breast cancer. In mid-2005, the WHO raised the International Agency for Research on Cancer (IARC) classification for COCs from "possibly" carcinogenic (IARC 1999) to a Group 1, or highest carcinogenic risk category. This agency concluded, "After examining all of the evidence, the Working Group classified combined oral contraceptives as carcinogenic to humans (Group 1)." Furthermore, the same Group 1 classification was made for "combined oestrogen-progestagen hormone therapy. The Working Group did not find evidence sufficient to infer a protective effect at any site" (Cogliano et al. 2005).

Furthermore, the 2005 WHO statement also concluded that in addition to being etiogenic for breast cancer, COCs are also Group 1 carcinogens for cervical and liver cancer (Cogliano et al. 2005). Other WHO-IARC Group 1 carcinogenic agents include arsenic, asbestos, and tobacco smoke.

The sequential use of both OCs and HRT compounds the risk of breast cancer. Women with a history of past usage of OCs, who are then re-exposed as older women when taking HRT, have a risk of 2.77 (95% CI, 1.44–5.32) (Lumachi et al. 2010).

A recent 2010 report from Harvard demonstrated a significant 33 percent increased risk of breast cancer among current users of OCs (multivariate RR, 1.33; 95% CI, 1.03–1.73). As noted in the abstract, "One specific formulation substantially accounted for the excess risk: the RR for current use of triphasic preparations with levonorgestrel as the progestin was 3.05 (95% CI, 2.00–4.66; $P < 0.0001$)" (Hunter et al. 2010).

Thus, it is truly concerning that levonorgestrel, the sole ingredient of Plan B, was made available without a prescription (over-the-counter, OTC) on Aug 24, 2006, in the United States for so-called "emergency contraception." Therefore, a 17-year-old male could buy it for a 15-year-old girlfriend. On Apr 30, 2013, the FDA lowered the OTC age to 15 years, but that was still insufficient. On Jun 20, 2013, all ethical, medical and legal restrictions collapsed; all age restrictions were dropped for Plan B One-Step (FDA 2013).

While adult baseball stars who take performance enhancing hormones are investigated by Congress, then received enormous fines and suspensions, the FDA approved massive amounts of hormones—Plan B One-Step (levonorgestrel) for OTC status "for all women of childbearing potential." This June 2013 FDA ruling was reported to comply "with the April 5, 2013 order of the United States District Court in New York" (FDA 2013).

Webster's dictionary defines "*woman*" as "*an adult female human being*" (Webster's Dictionary 2002, s.v. woman). This judicial/regulatory redefinition of all females who are physically capable of childbearing as "women," erases the distinction between children and adults. Perhaps, the FDA should have more transparently announced the unrestricted release of Plan B for all females, both children and adults, of "child-bearing potential." Ultimately, the

redefinition of children as women is more than a loss of an obvious distinction; it is a loss of protection for children (and adolescents).

Although it can now be purchased by a child of any age as easily as candy, Plan B One-Step is equivalent to the ingestion of 40–50 OCs at one time (FDA 2013).[10] Regrettably, there is substantial evidence that POCs, including levonorgestrel, are as carcinogenic as COCs, and likely more so.

Yager and Davidson (2006) in their authoritative review state "progestins tend to increase cell proliferation," which is a known mechanism for carcinogenesis. The Collaborative Study of more than 150,000 subjects found that POCs were used by women primarily in UK, Scandinavia and New Zealand. All told, only 0.8 percent of women (1253) used these agents in this immense report (Collaborative Group 1996).

This Collaborative Study reported a 1.17 RR of breast cancer among those using POCs within the prior 5 years to be "broadly similar to those for combined OCs" (Collaborative Group 1996).

Likewise, a Norwegian-Swedish cohort study found a similar increased breast cancer risk among women who were current or recent users of OCs (RR, 1.5 (COCs); 95% CI, 1.0–2.0 versus RR, 1.6 (POCs); 95% CI, 1.0–2.4). More worrisome, however, were the findings of increased risk (RR, 1.3; 95% CI, 1.0–1.7) for "short-term" users (i.e., "less than 13 months") of POCs before age 20 and before the FFTP (RR, 1.4; 95% CI, 1.0–1.8). Moreover, "long-term users of OCs were at a higher risk of breast cancer than never users (test for trend, $P = 0.005$)." These researchers concluded that the use of COCs and POCs "seem to increase the risk [for breast cancer] at the same level" (Kumle et al. 2002).

There is, in fact, reason to suspect that the progestins, such as levonorgestrel (Plan B), are more carcinogenic than CHRT. The 1995 *Nurses' Health Study* demonstrated the RR of breast cancer to be 1.5 among post-menopausal women on estrogen plus progestin, but 2.40 among women receiving progestin alone (Colditz et al. 1995). Similarly, the WHO-IARC (2007, 2876) final version of data released in 2005, although veiled, is revealing: "The addition of progestogens appears to enhance significantly the modest increase in the rate of breast cell proliferation caused by estrogen-only therapy. This is consistent with the notion of an increase in risk for breast cancer associated with combined estrogen–progestogen menopausal therapy, over that associated with estrogen-only menopausal therapy" (WHO-IARC 2007, 2876; Grosse et al. 2009).

Thus, the WHO-IARC concludes that the breast cancer risk of the estrogen component is "modest," but the addition of the progestogen (i.e., progestin) component "enhance[s] significantly" breast cell proliferation and breast cancer risk (WHO-IARC 2007, 2876; Grosse et al. 2009). As noted in Fact 6, a 2012 HRT report examined the risk of estrogens alone for the treatment of women with history of hysterectomy and climacteric symptoms. This report concludes that the "use of oestrogen for a median of 5.9 years (2.5–7.3) was associated with lower incidence of invasive breast cancer" (Anderson et al. 2012). The focus of CHRT is increasingly on the progestin component, and levonorgestrel (the sole ingredient of Plan B/Plan B One-Step) is a quite potent progestin. The OR of developing breast cancer among women taking progesterone-derived progestogens for HRT was 1.47, but the OR for women taking either norethisterone- or levonorgestrel-derived progestogens was significantly higher at 2.27 (95% CI, 1.98–2.62, $P < 0.003$) (Flesch-Janys et al.

2008). A review of progestogens (139 references cited) and the risk of breast cancer, by Campagnoli et al. (2005) ranked the progestogen potency of levonorgestrel in the fifth and highest group.

With notable candor, a 2010 report in *Contraception* states, "emergency contraception research has shifted from examining the public health effects of increasing access to emergency contraceptive pills (ECPs) to bridging ECP users to a regular contraceptive method as a way of decreasing unintended pregnancies" (Chin-Quee et al. 2010). This shift occurred as multiple studies, including two meta-analyses, failed to find the much anticipated huge reduction in unintended pregnancies, or the also predicted 1,000,000 reduction in surgical abortions from easier access to EC (Trussell, Schwarz, and Gutherie 2008). Trussell, Schwarz, and Gutherie conceded that OTC ECPs have been "no easy fix."[11]

Once again, continuous OCs are the contraceptive "focus," as they were in the 1960s. Nonetheless, the powerful progestin-only (levonorgestrel) so-called ECP (Plan B One-Step) is now available to U.S. children without a prescription (OTC), without *any* age restriction, and without parent or guardian consent.

In summary, the commonly prescribed COCs are WHO-IARC Group 1 carcinogens for breast cancer (Grosse et al. 2009). The occasionally U.S. prescribed-POCs are at least comparable in breast cancer risk to the COCs (Collaborative Group 1996; Colditz et al. 1995; Kumle et al. 2002; Campagnoli et al. 2005; Yager and Davidson 2006; WHO-IARC 2007, 2876; Flesch-Janys et al. 2008; Hunter et al. 2010). Moreover, a 2008 German review of progestins and breast cancer has concluded that, as has occurred with the progestin component of CHRT (Fact 6), "The previous assumption that progestin does not promote breast cancer development needs to be re-examined since a growing body of evidence indicates the opposite is true" (Giersig 2002).[12] The progestin-only Plan B One Step is a massive dose of the progestin, levonorgestrel, and is now available OTC to all U.S. children as a single-pill EC.

## Fact 8: There Is Worldwide Evidence for a Link Between Induced Abortion and Breast Cancer (ABC Link)

Even the Susan G. Komen Foundation does now (quietly) recognize that "birth control pill use" is a risk factor for breast cancer. Regardless, Komen and the ACS still deny that abortion is also a risk factor for breast cancer (American Cancer Society 2012; Komen 2012). In their meta-analysis of the ABC issue, Brind et al. noted, "Experimental evidence of a causal association between induced abortion and breast cancer in rodents was presented by Russo and Russo in 1980" (Russo and Russo 1980; Brind et al. 1996).

Additionally, there has been a recent and remarkable increase in the evidence for an ABC link, especially from non-Western countries.

- Bangladesh (2013)—A recent case–control report from the Dhaka Medical College (Bangladesh) employed a multivariate analysis. Women in Bangladesh are reported to have very traditional reproductive patterns, as Professor Joel Brind of Baruch College, City University of New York, explained, "Almost all the women are married (97% married, and the rest widowed) and with child by the time they are 20, and all of the kids are breastfed. Ninety percent had their first child at age 21 or younger (99% of controls did). They typically neither take contraceptive steroids nor have any

abortions. Nulliparty (childlessness) or abortion before first full-term pregnancy (both of which mean no breastfeeding) in a population in which breast cancer is almost unheard of, makes the relative risk very high" (Jabeen et al. 2013).

Among the factors found by the Bangladesh researchers to be protective against breast cancer were parity of 2 or more (OR = 0.29; i.e., 71% lower risk), longer duration of breast feeding (OR = 0.30), and giving birth at an early age (OR = 0.35). Among the factors that were found to be associated with an increased risk of breast cancer were current smoking status (OR = 6.78), personal history of breast cancer (OR = 10.99), family history of breast cancer (OR = 2.21), higher education (OR = 1.72), "personal income" (OR = 5.71), and OC users (OR = 1.47). The most notable finding, however, was that a "history of induced abortion" increased the risk of breast cancer more than 1900 percent (OR of 20.62). Brind calculates the 95% CI to be an unprecedented 12.85–32.51 (Ertelt 2013).

- China (General comments). One-fifth of the world's women live in China. Incidence rates of breast cancer there, as with Asian women in general, have traditionally been low, especially in rural areas. For instance, the rural county of Qidong has a breast cancer incidence of 12.8 per 100,000 women, "which is approximately one-tenth that of white women in the United States" (Linos et al. 2008). Nonetheless, "the incidence of breast cancer in China has increased at an alarming rate over the past two decades (from 36.17/100,000 to 51.24/100,000 in urban areas and from 10.39/100,000 to 19.61/100,000 in rural areas" (Huang et al. 2013). Overall, Chinese incidence rates are expected to climb from the current 10–60 per 100,000 women to "more than 100 new cases per 100,000 women aged 55–69 years by 2021" (Linos et al. 2008).

These U.S., British, and Chinese researchers note that, "Shanghai, Hong Kong, Japan and Singapore have recently experienced rapid increases in breast cancer." "Furthermore, breast cancer incidence among Asian-American women is increasing: Rates in Japanese-American women surpassed the age-specific rates in white US women" (Linos et al. 2008). These changes have occurred "because of shifts in risk factors of younger women" and these multi-national researchers concluded, "China is on the cusp of a breast cancer epidemic" (Linos et al. 2008).

China (2002)—An early 2002 cohort study of the relation of breast cancer to IAs in Chinese women found that, "Abortions as they have been performed in China are not an important cause of breast cancer." Nonetheless, these researchers noted that abortion, although "widely used in China since the 1970s" as part of the state's one child per family program would be an abortion prior to a first birth, and would also likely to have occurred prior to marriage. Such abortions would be "less socially acceptable" and "not as likely to be reported in an interview." Such a cultural norm creates a potential for recall bias via abortion under-reporting, and could have contributed to this early Chinese finding of no ABC link (Ye et al. 2002).

These researchers did note that a "non-significant increase in risk was observed in our case-control study in women who had undergone an IA at gestational week 10 or later; and this apparent relationship was especially strong for abortions before a first birth" (Ye et al. 2002). Subsequent data from China strongly link IA to its emerging breast cancer epidemic.

China (2010)—A more recent study from Northeast China found a "family

history of breast cancer and induced abortion [IA] increased the risk of breast cancer." Additionally, "breastfeeding protected parous women from any subtype of breast cancer" (Xing, Li, and Jin 2010).

China (2012)—Researchers in the Chinese east coast province of Jiangsu found that Chinese women who had $\geq 3$ IAs, had a risk that was nearly 2.5 times (141% increased risk; OR, 2.41; 95% CI, 1.41–4.42) that of women who had not had an abortion. Both premenopausal and postmenopausal Chinese women exhibited a significant "dose–response" trend in the number of IAs (P for trend: 0.0001). This report concludes, "induced abortion may play an important role in the development of breast cancer in Jiangsu women of China" (Jiang et al. 2012).[13]

China (2013)—In late 2013, a meta-analysis of 36 Chinese studies found a significant association between IAs and breast cancer (OR = 1.44, 95% CI 1.29–1.59, $P < 0.001$). Thus, the risk was increased 44% with one IA. These researchers also found evidence of a dose–response risk. At least two abortions increased the risk 76% and "at least at three" IAs increased the risk 89% (both results were highly significant, $P < 0.001$) (Huang et al. 2013).

- India (2008)—Indian researchers reported that the mean number of abortions among cases of breast cancer was nearly twice that reported in controls (1.02 v. 0.52, t = 2.35, $P < .05$) (Rai et al. 2008).

India (2013)—Likewise, a current study from the sub-continent of India found a marked 6.38-fold increased risk of breast cancer among women with IAs (OR 6.38; 95% CI, 0.99–40.81, $P = 0.05$). This finding was significant ($P < 0.05$) in the univariate analysis and of borderline significance in the adjusted analysis. This study had limited power, as there were only 84 cases and controls. All told, eight suspected risk factors for breast cancer were examined. A vegetarian diet was protective in the adjusted analysis, but a family history of breast cancer was not found to be a significant risk factor (even in the univariate/unadjusted results) (Kamath et al. 2013).

India (2013)—Another case–control study of reproductive factors and breast cancer from an Indian tertiary care hospital (New Delhi) was published in late 2013. In an initial univariate analysis, a higher age at menarche (≥16 years, OR = 2.76), later marriage (≥21 years, OR = 2.69), delayed childbirth (≥22 years, OR = 2.15), later age for last childbirth (≥28 years, OR = 3.29), being menopausal (OR = 2.50) and later age of menopause onset (≥50 years, OR = 2.68) were all significant risk factors for breast cancer. Nonetheless, the higher risk factors were: history of abortions (OR = 6.26), history of OC pills (OR = 9.50), and shorter duration of breastfeeding (<12 months, OR = 14.9). A family history of breast cancer "was reported in 21.3 percent of cases and none of the controls." Lastly, in a multiple logistic regression the remaining four significant associations were age at last childbirth (OR = 8.87), duration of breastfeeding (OR = 5.91), history of abortions (OR = 5.03), and age (delayed child bearing) at first childbirth (≥22 years, OR = 5.26) (Bhadoria et al. 2013).

India, with a population in excess of one billion, approximates China's standing as home to nearly one-fifth of the world's population. Large increases in breast cancer rates in these two nations substantially raise the global burden from this disease.

- Iran (2007)—Researchers at Tehran University conducted a case control study more than a decade ago (2000–

2002) that did not find a relationship between breast cancer and either IA or OCs (Mahouri, Dehghani Zahedani, and Zare 2007).

Iran (2011)—However, another group of Iranian researchers recently found breast cancer to be the most common cancer in women and its "prevalence is increasing annually by 2 percent" (Motie et al. 2011).

Iran (2011)—As has been the case with China and India, more recent data from Iran clearly affirms the ABC link. In 2011, Iranian researchers concluded, "Nulliparity, late age at first birth and abortion were the most important reproductive factors associated with breast cancer risk" (Hajian-Tilaki and Kaveh-Ahangar 2011). Incredibly, Muslim women having five or more babies reduced their risk of breast cancer by 91 percent. Each "additional parity" (baby) was found to reduce the risk by 50 percent.

This Iranian report also affirmed MacMahon's seminal investigation. First birth at age of 20 or less, breast-feeding, and breast-feeding for ≥24 months were all factors associated with a decreased risk of breast cancer. A remarkable protective dose–response from prolonged breast-feeding was found among these Iranian women. The adjusted ORs for breast-feeding for 13–24, 25–48, and ≥49 months were 0.39, 0.23, and 0.09, respectively.

These equate to 61, 77, and 91 percent respective reductions in breast cancer risk in these three groups (Hajian-Tilaki and Kaveh-Ahangar 2011).

These Iranian researchers summarized their etiological conclusions: "The reason for increasing of its (breast cancer) incidence during two recent decades in Iran probably is due to changes and tendency toward western life style in the pattern of reproductive factors and other lifestyle-related factors that are responsible for breast cancer risk" (Hajian-Tilaki and Kaveh-Ahangar 2011). For the modern Western woman, the Pill is the frequent path to delayed childbearing and nulliparity.

- Japan (1957)—Historically, a seminal 1957 report from Japanese researchers found a relationship between abortion and breast cancer (Segi et al. 1957).
- Pakistan (2011)—A breast cancer investigation at the teaching hospital in Karachi (Pakistan) found that older patients generally presented with a "low tumour grade," a hormone receptor positive status, and a lower percentage with "lymph node metastasis." As has been recently noted in American women (Johnson, Chien, and Bleyer 2013), newly diagnosed breast cancer patients who were age 40 or younger, "presented in significantly high percentage with advanced disease including high tumour grade and lymph node metastasis" (Raza et al. 2011).[14]
- Russia (1989)—An epidemiological study in the former USSR has likewise found a significant association between abortion rates and incidence of breast (and cervical) cancer (Remennick 1989).
- Sri Lanka (2010)—Breast cancer is the "commonest malignancy among women in the world as well as in Sri Lanka." The incidence there has more than doubled from 4.6 per 100,000 women in 1985 to 9.8 in 2005. A case–control study conducted by researchers at the University of Colombo (Sri Lanka) examined 18 potential risk factors. Upon adjustment with multiple regression modeling, only the "controversial risk factor," "having an abortion" in the past (OR, 3.42; 95% CI, 1.75–6.66), and passive smoking (OR 2.90), significantly increased the risk (De Silva et al. 2010). Again, a family history of breast cancer (see Kamath et al. 2013) was of

borderline significance in the univariate analysis, and not related to risk after adjustment. Breast-feeding significantly lowered the risk of breast cancer in a dose–response manner (De Silva et al. 2010).

- Turkey (2009)—Similarly, Turkish researchers, found 13 individual variables significantly related to breast cancer risk, but upon further analysis employing a multivariable logistic regression, this team found that only *age* (> or = 50 years) (OR, 2.61; 95% CI, 2.20–3.11) and IA (OR, 1.66; 95% CI, 1.38–1.99) to be significantly associated with breast cancer (Ozmen et al. 2009).

Table 5 contains a summary of the international data from this section. Prior to 2009, three of five of these reports found an ABC link. After 2009, 10 of 11 more recent reports found a positive ABC relationship, and one of these 11 recent studies is a 2013 meta-analysis of 36 Chinese reports (Huang et al. 2013).

Thus, an association between IA and breast cancer has been found by numerous Western and non-Western researchers from around the world. This is especially true in more recent reports that allow for a sufficient breast cancer latency period since an adoption of a Western life style in sexual and reproductive behavior. The average age for an abortion in the United States is in the early 20s and the median age for breast cancer diagnosis is 61 (Guttmacher Institute 2013; SEER 2013). A cohort study would therefore need to include four to five decades of data. Recall, as discussed in Fact 5, it was 60 years between the release of the hormone Premarin and the FDA black box warnings of 2002. Critiques of reports denying an ABC link are available (Brind et al. 1996; Brind 2013a, 2013b).

## Fact 9: There Is a Substantial Causality Case for an Induced Abortion–Breast Cancer link

As discussed in Fact 8, multiple research groups from around the world have found an association between IA and breast cancer. The Breast Cancer Prevention Institute has identified 70 published scientific reports on this topic, dating back to the 1957 Japanese study (Segi 1957). All total, 58 of these 74 international studies show a significant association between abortion and breast cancer, including 12 of the last 13 reports since 2008 (Breast Cancer Prevention Institute 2013a, 2013b).

As early as 1996, a review and meta-analysis by Brind et al. showed a 30 percent increase in breast cancer risk after the first pregnancy, but a 1.5-fold, or 50 percent increased risk before the first pregnancy. Both findings were statistically significant (Brind et al. 1996).

Recently, Oxford University researcher, Patrick Carroll, conducted another important epidemiological investigation on the Western epidemic of breast cancer. This multiple linear regression analysis, and multi-national 2007 study, examined a myriad of suspected variables. The conclusion was that abortion is so powerfully linked to breast cancer risk, that it is the single best predictor of the occurrence of breast cancer in all eight European countries studied. Carroll found that future breast cancer rates could be predicted with near 100 percent accuracy by using a nation's abortion rates, and its fertility rates ("also useful") (Carroll 2007).

The breast cancer rate in England and Wales is up 80 percent since 1971. By using actuarial modeling, Carroll predicted that the rate of breast cancer would further rise 50.9 percent during the next 25 years in these two countries, given their high abortion and low fertility rates. In contrast,

***Table 5*** *International reports of breast cancer risk factors*

| Report | Induced abortion | Oral contraceptive use | Older age | Family history of breast cancer | Delayed child birth | Reduced duration of breast feeding | Cigarette smoking exposure |
|---|---|---|---|---|---|---|---|
| *a. Reports before 2009: Abortion Breast Cancer (ABC) link found in 3 of 5 reports* | | | | | | | |
| China (Ye et al. 2002) | 0 | | | | | | |
| India (Rai et al. 2008) | + | | | | | | |
| Iran (Mahouri, Dehghani Zahedani, and Zare 2007) | 0 | 0 | | | | | |
| Japan (Segi et al. 1957) | + | | | | | | |
| Russia (Remennick 1989) | + | | | | | | |
| *b. Reports from 2009–2013: ABC link found in 10 of 11 reports* | | | | | | | |
| Bangladesh (Jabeen et al. 2013) | 4+ | 1+ | | 2+ | ↑ | ↑↑ | 3+ * |
| China (Xing, Li, and Jin 2010) | 1+ | | | 2+ | | | |
| China (Jiang et al. 2012) | 2+ | | | | | | |
| China** (Huang et al. 2013) | 1+ | | | | | | |
| India (Kamath et al. 2013) | 3+ | | | | ↑ | | |
| India (Bhadoria et al. 2013) | 3+ | 4+ | ↑ | | ↑ | ↑ | |
| Iran (Motie et al. 2011) | 0 | | | 2+ | | 0 | |
| Iran (Hajian-Tilaki and Kaveh-Ahangar 2011) | 2+ | | | | 3+ | ↑ | |
| Pakistan (Raza et al. 2011) | 2+ | | | 1+ | 1+ | | |
| Sri Lanka (De Silva et al. 2010) | 2+ | | | +/- | | ↑ | ↑*** |
| Turkey (Ozmen et al. 2009) | 1+ | ↓ | 2+ | 1+ | | | |

**Current smoking.*
***2013 meta-analysis of 36 Chinese reports.*
****Passive smoking.*
*Risk factors for Breast Cancer found to significantly increase (hazardous) or decrease (protective) risk in at least two of above international reports.*
*Note: 0 (No increase), ± borderline association, ↑ increased risk, ↓ decreased risk. Significant OR reported: 1+ (OR, <2), 2+ (OR, 2 to <4), 3+ (OR, 4 to <8), 4+ (OR, ≥8).*

with its high fertility and low abortion rates, Ireland is expected to see only an 8.3 percent increase in its breast cancer rate. Ironically, Professor Joel Brind traces the "safe abortion virus" that "abortion does not increase your breast cancer risk" to the same Oxford University, beginning in 1982 (Brind 2013a, 2013b).

In addition, the so-called "triple negative" breast cancer (negative for estrogen receptor, progesterone receptor, and human epidermal growth factor) is a particularly virulent subtype that is associated with "high mortality and inadequate therapeutic options." Of note, these researchers included abortion among the "known and

suspected" breast cancer risks for this particularly lethal breast cancer sub-type (Dolle et al. 2009).

A review and synthesis of the evidence for an induced ABC link is necessary before arriving at an ultimate conclusion of causality. Schlesselman (1982, 22–4) lists the six criteria for concluding causation: (1) *Temporal sequence*—IA does precede breast cancer, frequently by several decades or more. (2) *Consistency*—Data from animal and humans from multiple research centers around the globe have reached the same conclusion that IA is strongly linked to breast cancer (Segi et al. 1957; Russo and Russo 1980; Remennick 1989; Brind et al. 1996; Ye et al. 2002; Mahouri, Dehghani Zahedani, and Zare 2007; Rai et al. 2008; Ozmen et al. 2009; De Silva et al. 2010; Xing, Li, and Jin 2010; Motie et al. 2011; Raza et al. 2011; Bhadoria et al. 2013; Brind 2013a, 2013b; Ertelt 2013; Huang et al. 2013; Jabeen et al. 2013; Kamath et al. 2013; Linos et al. 2008; SEER 2013). (3) *Strength of association*—The strength of association is generally moderate to very strong (Jabeen et al. 2013), and consistently strong when IA(s) precedes the first pregnancy, or when there are multiple abortions. (4) *Biological gradient*—A strong "dose (IA)-response (breast cancer)" was noted in both the China (Jiang et al. 2012) and (Huang et al. 2013) reports. (5) *Specificity of effect*—As noted by Schlesselman, this requirement is frequently absent. In fact, an example of a chronic disease with only one cause is not easily called to mind. As is the case with most chronic diseases, breast cancer has multiple etiological risks. (6) *Collateral evidence and biological plausibility*—In the introduction to the 2013 meta-analysis, Chinese researchers note the "alarming" increased incidence of breast cancer in their country during the past two decades and call the ABC relationship "plausible" (Huang et al. 2013).

Additionally, as noted in the *British Journal of Cancer*, "during the early months of pregnancy, the mammary epithelium undergoes massive proliferation and this is followed by differentiation in preparation for lactation. It has been hypothesized that interruption of pregnancy before differentiation occurs would increase the risk of breast cancer" (Ye et al. 2002). Information on pathological breast development, as well as data from around the world provide support for this hypothesis (see Facts 5 and 8). The criteria for the conclusion that IA causes breast cancer appear to be fulfilled.

## Fact 10: Research Studies Document a Compounding of Breast Cancer Risk Factors for Girls and Young Women that Underscores the Duty for Full and Accurate Informed Consent

According to breast cancer surgeon, Dr. Angela Lanfranchi, a girl or young woman who undergoes an abortion, increases her risk of breast cancer in four ways: "[S]he creates in her breasts more places for cancers to start, which is an 'independent effect'; she loses the protective effect that a full-term pregnancy would have afforded her; she increases the risk of premature delivery of future pregnancies; and she lengthens her susceptibility window" (Lanfranchi 2009).

Not unlike cardiac risk factors (i.e., hypertension, cigarette smoking, diabetes mellitus, etc), having more than one risk factor compounds the risk of breast cancer via synergistic mechanisms. In the previously noted investigation of triple-negative breast cancer, women ≤ 40 years of age have an elevated risk that is 3.5-fold, if they began using OCs at age 22 years or later (Dolle et al. 2009). Those women who began OCs before age 18

years, nearly doubled this risk (6.4-fold risk). In fact, this multivariate analysis found that more recent OC usage and youthful usage were the strongest predictors of breast cancer, even surpassing a positive family history.

A similar compounding of risks factors was reported by Janet Daling et al. (1994) in the prestigious *Journal of the National Cancer Institute* in an investigation titled, "Risk of breast cancer in young women: relationship to induced abortion." A history of abortion before 8 weeks gestation in women younger than 18 years (girls) increased the risk of breast cancer by 30 percent. However, if a pregnancy lasting more than 8 weeks was terminated when a girl was younger than 18 years, the risk increased 800 percent (adjusted RR 9.0). Moreover, "[i]n women with a positive family history (defined as a sister, mother, aunt, or grandmother with breast cancer), the overall risk was 1.8" (80% increase), but "was particularly strong for a first abortion that occurred prior to age 18 years." In fact, the risk was infinity, as breast cancer developed in 100 percent of these girls—12 of 12 cases, but in none of the controls. There was, however, "no increased risk of breast cancer … associated with spontaneous abortions," RR = 0.9 (Daling et al. 1994).

Further evidence of a crack in the anti-ABC cultural dike comes from an unlikely source, Dr. Janet Daling herself. The Breast Cancer Prevention Institute quotes her poignant comments: "I have three sisters with breast cancer; I resent people messing with scientific data to further their own agenda, be they pro-choice or pro-life. I would have loved to have found no association between breast cancer and abortion, but our research is rock solid, and our data is accurate. It's not a matter of believing, it's a matter of what is" (Breast Cancer Prevention Institute 2009).

In 1987, the Seattle-Puget Sound Surveillance, Epidemiology, and End Results (SEER) cancer registry data for women aged 25–44 years revealed that the incidence of breast cancer had increased by 22 percent ($P < 0.001$) between the time periods 1974–1977 and 1982–1984. This research team, which included Daling, reported an annual increase of 2.5 percent ($P < 0.001$) (White et al. 1987).

This local finding has been recently confirmed nationally. In the *Journal of the American Medical Association*, Johnson, Chien, and Bleyer (2013) reported a "small but statistically significant increase in the incidence of breast cancer with distal involvement in the United States between 1976 and 2009 for women aged 25 to 39, without a corresponding increase in older women."

Karen Malec, president of the Coalition on Abortion/Breast Cancer, notes that advanced breast cancers in these young women climbed from 1.53 per 100,000 in 1976 to 2.90 in 2009—a "90 percent increase during a 33 year period." "It's utterly stunning, that Johnson's team called the increased incidence in advanced cancers in young women 'small,'" states Malec (Breast Cancer Prevention Institute 2013a, 2013b). Perhaps even more stunning is a quote by Rebecca Johnson, a pediatric & adolescent oncologist at Seattle's Children's Hospital, and an oncologist at the University of Washington, who is the first author of the accompanying *Journal of the American Medical Association* report. Johnson appeared to agree with Malec rather than with her own research team. When interviewed by *USA Today* about these sobering new breast cancer statistics in young women, Johnson conceded, "It's a big increase, and it is accelerating over time, and it's hitting the youngest women" (Szabi 2013).

Moreover, the incidence of metastatic breast cancer (i.e., to bone, brain, lungs,

etc.) showed the greatest increase among 25- to 34-year-old women, with the rate rising from 0.81 per 100,000 to 2.14 during this same 33-year period, a striking increase of 164 percent for a disease that is likely to be lethal at this stage. Johnson, Chien, and Bleyer (2013) also noted that the proportion of breast cancers occurring among Swiss 25- to 39-year olds, more than doubled from 3.5 percent of the total in 1995, to 7.2 percent in 2004.

The Johnson, Chien, and Bleyer (2013) report further explained that, "the rate of increasing incidence of distant disease is inversely proportional to age at diagnosis." Tragically, younger women have a poorer prognosis. Not only is the disease becoming more common among younger women, it is more likely to be metastatic at the time of diagnosis. The U.S. five-year survival for these young women with distant disease is only 25 percent (Siegel, Zou, and Jemal 2014).

As previously noted, the median age of breast cancer onset has been 61 years, and routine mammogram screening has begun at age 40 years. Nonetheless, Johnson, Chien, and Bleyer (2013) soberly concluded, "that an increasing number of young women in the United States will present with metastatic disease in an age that already has the worst prognosis, no recommended screening practice**,** the least health insurance, and the most potential years of life."

## Conclusion

More than 40 years ago, physician, "founder of modern epidemiology," and pioneer breast cancer researcher—Prof. Brian MacMahon—wrote almost prophetically, "One of the most important contributions of epidemiology to the fight against cancer has been the demonstration that many of the prevalent forms of human cancer are *preventable*" [Emphasis added] (MacMahon 1969).

To a large extent, the breast cancer epidemic is due to preventable factors. Modern epidemiology provides substantial evidence that a delay (or avoidance) of childbearing, as well as a reduced duration (or avoidance) of breast-feeding, increase the risk of breast cancer through a loss of natural protections.

Worldwide studies provide evidence of an emerging breast cancer pandemic. Additional preventable breast cancer risk factors include IA, especially one before the FFTP, and the ingestion of artificial female hormones, whether *as* OCs (especially when taken before the FFTP), CHRT, or both (Lumachi et al. 2010).

Given the evidence for a pandemic and breast cancer's known risk factors, it is reasonable to ask whether girls and young women, who are being prescribed an OC, are being properly informed of the potential harms. These risks[15,16] include a WHO affirmed increased rate of breast cancer, a *PDR*-acknowledged risk of implantation prevention (abortifacient action), as well as high blood pressure, heart attack, stroke, deep venous thromboses, pulmonary emboli, gallbladder disease, liver cysts and cancer, weight gain, headaches, depression, human papillomavirus, cervical cancer, and a doubling of HIV risk (Heffron et al. 2012; Peck and Norris 2012).

The strength of the breastcancer epidemiological evidence substantiates the necessity that all females receive full and accurate informed consent before they are provided hormones, IA, or both. This informed consent is especially imperative for a girl (and parent/guardian) or a young woman, who is in the pre-FFTP breast cancer "susceptibility window." As a family history of breast cancer, of which the child may be unaware, increases the risk for the girl considering an abortion (Daling et al.

1994), the presence of a parent may provide clinical information critical to accurate informed consent.

A duty to provide proper informed consent assuredly includes a young girl (and her parent or guardian), when a COC, a WHO Group 1 carcinogen, is prescribed by a physician for the treatment of acne. The prescribing of a known carcinogen to a child for any non-lethal disease is problematic. Such a practice without the provision of full and accurate informed consent for the girl, and at least one parent or guardian, is medically, legally, and ethically indefensible.[6]

Moreover, an OC, even when prescribed for a non-contraceptive purpose, frequently becomes a gateway drug or "bridge" to contraception, as the girl and her boyfriend mature. Contraception may also prepare the way for the growing, unwise, and actually dangerous practice of co-habitation (Schneider 2007).[17]

There is an established need for a greater awareness of preventable risk factors for breast cancer, especially the role of CHRT and COC hormones, and IA (Fact 8). The hormone replacement (HRT, Fact 6) story proves that prevention on a national scale is possible, especially when females are fully and accurately informed of the known risks.

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## Endnotes

1. A college co-ed was in one of the authors' (APSII) office in the fall of 2012 wearing a Susan G. Komen, "Race for the Cure" t-shirt. The upper back area read, "Breast cancer risk factors: being female and getting older." Barring a reprehensible sex-selection abortion, or a tragic premature death, neither is preventable.
2. As will be discussed in Fact 8, the epidemic of breast cancer is not confined to the United States, or other Western countries. Evidence exists for an actual breast cancer pandemic: the worldwide incidence of breast cancer has grown from 641,000 in 1980 to 1.64 million in 2010, "an annual rate of increase of 3.1 percent" (see Peck and Norris 2012).
3. Young, D.G. Young living hormone replacement therapy: a theory run amok. http://stonekingdom.org/articles/HRT.pdf. Things reportedly did not fare so well for Wilson who had once occupied a Fifth Avenue office, apparently another gift from Wyeth. It is also reported that his own son came to reject his writings. The FDA reportedly banned Wilson from certain research for making unsubstantiated claims and his wife reportedly died of breast cancer in 1988, after two bouts with the disease and a mastectomy.
4. Progestins belong to three main chemical families: progesterone derivatives, testosterone/19-nortestosterone derivatives, and a spironolactone derivative (see Bengiano, Primiero, and Farris 2004) The *Medical Letter* has recently reviewed the relation of testosterone supplementation to cardiovascular-events. There is a growing body of

clinical evidence demonstrating an increased CHD risk from this hormone including a meta-analysis (OR = 1.54; 95% CI, 1.09–2.18). An analysis by funding source found the risk was greater in trials not funded by the pharmaceutical industry (OR 2.06 vs. 0.89) (see Anonymous 2014).

5. As late as the 2004 edition of the *PDR*, the official wording on Premarin listed 41 "adverse reactions" in 8 systems, but the section on breast did not mention cancer, but listed only "breast tenderness and enlargement" (see *Physicians' Desk Reference* 2004, s.v. Premarin). The 2005 edition, however, did discuss the WHI findings in a FDA's highest ("black box") warning of "increased risk of myocardial infarction, stroke, invasive *breast cancer*, pulmonary emboli and deep vein thrombosis in post-menopausal women" (see *Physicians' Desk Reference* 2005, s.v. Premarin).
6. In fact, the FDA issued a "warning letter" to Bayer on October 3, 2008, noting,

   "In addition, the TV ads suggest that YAZ is approved for acne of all severities when this is not the case.…The word 'ACNE' appears in large print in the middle of the screen along with the audio claim 'It can also keep your skin clear,' which is accompanied by a close-up visual of a woman with completely clear skin. Similarly, in [the TV ad] 'Balloons,' the 'ACNE' balloon is prominently displayed on the screen as it floats by a smiling woman with obviously clear skin, along with the audio claim that YAZ '…also helps keep skin clear.'"

   The FDA finds this to be a misleading impression created by audio and visual claims in the TV ads that YAZ is indicated for acne of all severities. The FDA finds both the advertising for Premenstrual Dysphoric Disorder (PMDD) and Acne to *be "Broadening of Indication"* and "*Overstatement of Efficacy*" violations. The FDA further notes that the "Not Gonna Take It" ad utilizes fast-paced visuals depicting women, "looking at pictures, trying on clothes, chatting at a café." "Balloons" depicts various "women running in the park, sitting on a scenic waterfront, smiling, walking out of coffee shop … walking through the street to join friends, in addition to a pigeon on a building ledge and balloons being released and floating away. These complex presentations distract from and make it difficult for viewers to process and comprehend the important risks being conveyed. *This is particularly troubling as some of the risks being conveyed are serious, even life-threatening. The overall effect of the distracting visuals, graphics, concurrent supers and background music is to undermine the communication of important risk information, minimizing these risks and misleadingly suggesting that YAZ is safer than has been demonstrated by substantial evidence or substantial clinical experience*" (emphasis added). Bayer was asked to immediately "cease dissemination of violative promotional materials for YAZ that are the same as or similar to those described above." See Thomas Abrams, director, Division of Drug Marketing, Advertising, and Communications. U.S. Department of Health and Human Services Food and Drug Administration, to Reinhard Franzen, president and CEO, Bayer HealthCare Pharmaceutical, Inc., re: NOA #21-676,21-873,22-045 YAZ (drospirenone and ethinyl estradiol) Tablets, MACMIS 10# 16473, October 3, 2008. http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/EnforcementActivitiesbyFDA/WarningLettersandNoticeofViolationLetterstoPharmaceuticalCcompanies/ucm053993.pdf. The rate ratio for venous thromboembolism (VTE) among drospirenone-containing OC users ranged from 4.0 to 6.3 compared with non-users of OCs. (See Wu et al. 2013).
7. Edgren, Jones, and Peterson (1967) address the topic of pregnancy maintenance with the 13 agents in this report. They report that, "spaying of pregnant rats is normally followed by abortions" but administration of the "progestogens, progesterone and acetoxyprogesterone derivatives were active" [the pregnancies were maintained], whereas norethylnodrel and norethisterone were inactive [rat abortions occurred]; estrone and testosterone were also inactive. "Active" agents were said to show "true" progestational effects. Nonetheless, agents that maintained the spayed rat pregnancies, as well as those

that did not, were classified as "progestational" agents. The incoherence is obvious. Edgren later published a review transparently titled, "Progestogens as contraceptives." (see Edgren 1974). Contraceptives are not pro-gestational.

8. Sitruk-Ware correctly states that, "Very small structural changes may account for considerable changes in the effects of progestins." A single substitution at the ß-position of the carbon 17 of the steroid nucleus transforms progesterone to testosterone. Historically, in vivo tests of the progestational activity of progestins, have been the McPhail Index (the dose of progestin required to transform the E-primed endometrium to the secretory state) and the pregnancy maintenance test (the progestin dose required maintain a pregnancy in a ovariectomized female rat). (See Sitruk-Ware 2006). OCs, in the form of progestins, do not support pregnancy in the human female whose ovaries have been surgically removed. These "common characteristics" of the progestins in rats have no relevance in humans.
9. An example of a totally inaccurate claim imputing a progesterone-class effect to a progestin is Dr. Sandra Reznik's statement in the February 2010 issue of *Health Progress,* a publication of the Catholic Health Association (http://www.chausa.org), regarding Plan B (levonorgestrel), "[L]evonorgestrel is an artificial progestin —a synthetic hormone compound with a structure and function similar to the female hormone progesterone. *Progestin helps to make the uterus more receptive to implantation and helps maintain pregnancies*" (emphasis added). (See Reznik 2010).
10. FDA (2013, June 20). Plan B One-Step is the 1.5 mg of levonorgestrel (LNG) single-dose successor of two-dose 12 hour apart (0.75 mg each) Plan B. Plan B is equivalent to taking 40 Ovrette birth control pills (available in the U.S. until 2005; each pill contains 0.075 mg of norgestrel, half of which is an active isomer, or the equivalent of 0.0375 mg of LNG). See *Physicians' Desk Reference* (2005, s.v. ovrette), or 50 internationally distributed Microlut birth control pills. Auckland NZ: Bayer New Zealand; *Information for health professionals*: Microlut [0.03 mg LNG]. As the usual birth control pill packet contains 21 active pills and 7 blanks, a two months supply of Microlut contains 42 pills and 14 blanks. Thus, Plan B is equivalent to nearly two and half months of the Microlut birth control pills. Moreover, the sole ingredient of the synthetic progestin Plan B, *levonorgestrel, is 4,000 times as potent as the natural hormone, progesterone* (see Stanczyk et al. 2013). How many other conditions are properly treated by competent and ethical physicians advising their pediatric patient to take a handful (the equivalent of 40–50) powerful synthetic sex hormone pills? The availability to children of super-sized soft drinks receives much media attention, but the unrestricted availability to children of unprecedented doses of potent carcinogenic sex hormones receives no media attention.
11. Trussell, Schwarz, and Gutherie stated: "A decade ago, emergency contraception (EC) captured the imagination of the reproductive health world. Here, we thought, was an 'easy fix' that would revolutionize our age-old relationship with unprotected sex and unintended pregnancies. Initial projections of widespread use of EC included *dramatic reductions* in the need for abortion services. Public health campaigns dedicated to allowing over-the-counter access to EC *have rallied large numbers of grass-roots activists*. Unfortunately, the return on this investment of time, energy and money has been disappointing. Multiple randomized clinical trials have been conducted in an effort to demonstrate that increasing access to emergency contraceptive pills (ECPs) can reduce rates of unintended pregnancy or abortion, but to date, *none of the interventions tested has had a significant effect on rates of either pregnancy or abortion.* Even a comprehensive review and a meta-analysis of the available trials were unable to show any significant impact of increased access to EC on clinically relevant outcomes such as pregnancy or abortion" (emphasis added).
12. Giersig notes that data from the German adverse drug reactions database shows that reported breast cancer cases on OCs include 111 women who had been on POCs and 12 cases on COCs (9.25-fold more for POCs than COCs). This

statistic is even more remarkable when one considers that use of POCs is "calculated to be 20 times lower" than COCs. This represents more than a 180-fold overrepresentation of breast cancer cases associated with POC vs. COC usage.

13. A calculated odds ratio (OR) approximates the relative risk (RR). A RR of 1.5 is a 50% increased risk, 0.5 is a 50% decreased risk, and a RR of 3.0 is a tripling of risk (i.e., a 200% increased risk).
14. On October 5, 2013, the local newspaper in Lexington, Kentucky published "The Pink Paper: Breast Cancer Awareness" edition for the third consecutive year. At the top of the front page was an article announcing a new local support group for young women with breast cancer (see: Meehan 2013). In fact, two such groups have recently begun in Lexington.
15. Traditionally, POCs have been thought to be associated with a lower risk of blood clots. It is now established, however, that the blood clot risk is substantially increased for users of newer OCs that contain the fourth generation progestin, drospirenone. The RR for venous thromboembolisms (VTEs) among drospirenone-containing OCs users ranged from 4.0 to 6.3 compared with non-users of OCPs (see: Wu et al. 2013).
16. Peck and Norris note a tenfold higher risk of myocardial infarction for women who take OCs and smoke. The risk after age 35 for smokers who take OCs is even higher. They also report that women who have a hereditary thrombophilia condition, such as Factor V Leiden are "*ticking time bombs*." These women who use OCs have *an increased risk of* deep vein thromboses *that is thirty-five times higher* than women who do not have this mutation. Peck and Norris further note that Ortho Evra is a contraceptive transdermal patch that has been associated with an increased risk of pulmonary embolism, as it "delivers a higher dose of estrogen into the circulatory system by avoiding 'first pass' metabolism by the liver." Relative to the disputed abortifacient action of levonorgestrel (LNG, Plan B), Russian researchers administered LNG 9 h (or more) postovulation. The clinical pregnancy rate was reduced from 92% in the control group of baboons (11 of 12) to 10% (2 of 20) for those receiving LNG—an 89% reduction, which is exactly the FDA approved manufacturers reported efficacy rate for Plan B. These WHO funded researchers accurately described this action as an interceptive effect, which they defined as processes that "reliably interfere with some of the procedures preceding implantation" (see Oettel et al. 1980).
17. Co-habitation has grown 11-fold increase since the 1960s and is associated with a *nine-fold greater murder rate* for co-habiting females (Schneider 2007).

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Nancy K. Mullen, MD, is board certified in internal medicine. She is a leader in the Catholic Way Bible Study and Assistant Clinical Professor at the University of Kentucky Medical Center, where she provides primary care for HIV patients. She is a wife and mother of three children and president of the SS. Luke and Gianna Guild of the CMA.

Amberly K. Windisch, MD, is a board-certified urologist. She is a convert to the Catholic faith, mother of four children, member of the SS. Luke and Gianna Guild of the CMA, and currently Clinical Assistant Professor at the University of North Carolina (Chapel Hill).