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## REVIEW

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# The risk of breast cancer following spontaneous or induced abortion

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To evaluate the relationship between breast cancer risk and spontaneous and induced abortion, we conducted a detailed descriptive review of 32 epidemiologic studies that provided data by type of abortion and by various measures of exposure to abortion – number of abortions, timing of abortion in relation to first full-term pregnancy, length of gestation, and age at first abortion. Breast cancer risk did not appear to be associated with an increasing number of spontaneous or induced abortions. Our review also suggested that breast cancer risk probably was not related to the other measures of exposure to abortion, and probably did not differ by age or a family history of breast cancer. Finally, the data appeared to suggest a slightly increased risk among nulliparous women, but this tendency was based primarily on studies with a small number of nulliparous women who had had spontaneous or induced abortions. Definitive conclusions about an association between breast cancer risk and spontaneous or induced abortion are not possible at present because of inconsistent findings across studies. Future investigations should consider prospective designs, separate analyses of spontaneous and induced abortions, appropriate referent groups, and adequate adjustment for confounding and effect modification. Future investigations also should attempt to determine whether any increased risks reflect the transient increase in breast cancer risk hypothesized for full-term pregnancy or a causal relationship specific to spontaneous or induced abortion. *Cancer Causes and Control* 1997, 8, 93-108

**Key words:** Abortion, breast cancer, pregnancy, women.

### Introduction

In the United States in 1991, the number of spontaneous abortions among women with clinically recognized pregnancies was estimated at 896,000.<sup>1</sup> The rate for women aged 15 to 44 years was 15.2 per 1,000 women, and the highest rates were for women aged 25 to 29 years (22.3) and women of races other than White (20.4). For women whose pregnancies continue for eight to 28 weeks, the probability of pregnancy loss ranges from eight to 12 percent.<sup>2</sup>

In 1993, more than 1.3 million induced abortions were reported to central health agencies in the US, and the rate of induced abortion per 1,000 women aged 15 to 44 years was 23.<sup>3</sup> The rate of abortion in other countries ranges from 5.3 in the Netherlands to 111.8 in the former Soviet Union.<sup>4</sup> In the US, most women who had an induced abortion were young, White, and unmarried, and 47 percent had had no previous livebirths.<sup>3</sup> About 24 percent of all clinically recognized pregnancies end as induced abortions.<sup>1</sup>

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Breast cells have been hypothesized<sup>5</sup> to be the most susceptible to transformation into malignant cells when breast tissue contains primarily rapidly growing and undifferentiated epithelial cells – *i.e.*, during adolescence and pregnancy. That is, the number of undifferentiated cells increases when rapid growth in breast epithelium occurs, and by the third trimester, differentiation of breast cells reduces the number of undifferentiated cells that are susceptible to malignant transformation.<sup>6</sup> Some investigators have hypothesized<sup>5,7-9</sup> that the termination of pregnancy in the first two trimesters may alter the carcinogenic potential of breast tissue by interrupting the complete differentiation of breast cells that occurs during full-term pregnancy and confers protection. The effects of full-term pregnancy on breast cell differentiation have been examined in laboratory studies of breast tissue from mammoplasties, autopsies, and modified radical mastectomies among women with and without breast cancer, while the effects of an interrupted pregnancy have been studied only in rat mammary tissue.<sup>7-9</sup>

Numerous epidemiologic studies have examined the relationship between breast cancer risk and spontaneous and induced abortion and have reported conflicting results.<sup>10-11</sup> A study that was designed specifically to examine these relationships<sup>12-13</sup> renewed interest in this subject with the report of a possible relationship between induced abortion and breast cancer diagnosed before age 46. To establish a framework for the evaluation of new study findings, we conducted a descriptive literature review of the relationship between the risk of breast cancer and spontaneous or induced abortion.

## Materials and methods

We used computer-based searches and bibliographies of published articles to identify studies with information about the relationship between breast cancer and abortion published through January 1996.<sup>12,14-71</sup> We grouped studies by type of abortion and by several measures of exposure to abortion – number of abortions, timing of abortion in relation to the first full-term pregnancy, length of gestation, and age at first abortion, as well as by factors that potentially could modify the relationship between breast cancer risk and abortion – parity status, age of study participant, and family history of breast cancer.

We included in Table 1 all studies that provided some data separately for women who had had spontaneous or induced abortions.<sup>12,39,41-55,57-71</sup> We did not include two studies: an ecologic study,<sup>56</sup> and a study<sup>40</sup> that categorized pregnancies according to method of delivery – *i.e.*, spontaneous abortions were combined with spontaneous (as opposed to caesarean) deliveries; and uterine dilatation and curettages for abortion were combined with the deliveries of fetuses when instruments were used.

We included in Figures 1-4 a subset of the studies described in Table 1. The figures included all studies that provided data by type of abortion (spontaneous *cf* induced) and by specific measures of exposure to abortion (number of abortions and timing of abortion with respect to first full-term pregnancy) or by factors that may modify the relationship between abortion and breast cancer (parity status and study participant's age). Estimates of the relative risk (RR) are odds ratios for case-control studies and rate ratios for cohort studies. For Figure 4, risk estimates are arranged in order by age of study participant within the categories less than 46 and 46 or more years. We caution the reader that some subgroups in our figures may contain more than one risk estimate from the same study, and we have footnoted the specific subgroups. In individual studies, the RRs were adjusted by differing risk factors for breast cancer; Table 1 may be consulted for information about the specific variables that were considered as potential confounders or effect modifiers in each analysis.

We adopted several rules for including specific risk estimates in the figures. If a particular study reported both adjusted and unadjusted estimates, only the adjusted estimates are presented. If the study reported both Mantel-Haenszel and multivariate regression estimates, only the multivariate estimates are presented. For Figures 1-2 and 4, RRs are for parous or gravid women if the study only reported separate estimates for nulliparous (nulligravid) and parous (gravid) women for the exposure measure of interest. Similarly, for Figures 2-4, RRs are for women who had one abortion if the study only reported separate estimates for women who had one abortion and more than one abortion for the exposure measure of interest. The latter two rules focussed on the largest subgroups to enhance comparability with the other studies in the figures that included all women. Some investigators published several analyses from the same study over time and incorporated additional cases and controls.<sup>42-43,51,58-60</sup> For this situation, we included only the most recent data for each measure of exposure to abortion in the figures. Risk estimates by number of abortions from the most recent update of a study from Italy<sup>60</sup> were not included because they were nearly identical to the previous analysis and because they did not include confidence limits; instead we graphed the estimates from the previous analysis.<sup>59</sup> One analysis combined data from six case-control studies conducted in three countries.<sup>70</sup> We included in the figures only the RRs for the combined data; we did not include the RRs from the individual studies except for the two studies that had previously published RRs for the relationship between abortion and breast cancer.<sup>47,63</sup> We computed test-based 95 percent confidence intervals (CI)<sup>72</sup> for one study.<sup>45</sup>

We have organized our review by three design and