



NEWS, VIEWS AND COMMENTS

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New breast cancer research: mothers and twins

Twin studies have reported low concordance rates for breast cancer, for both identical (15%) and fraternal (10%) twin pairs.¹ These data demonstrate modest genetic influence on this condition, while highlighting a significant contribution from environmental factors. Identical twins clearly show less resemblance for breast cancer than would be predicted on the basis of their genetic identity. The message is that medical efforts must be directed toward identifying the crucial environmental triggers of this deadly disease and how they provoke cancer in predisposed genotypes. Twin studies of some other major medical conditions have yielded similar conclusions.²

Even more remarkable information emerged from breast cancer research released in February 2000. Investigators at the Mayo Clinic Cancer Center, in Rochester, MN, found that fraternal female twins with twin sisters face a significantly higher risk for breast cancer than identical twins, female twins with twin brothers, and singletons.³ Female twins with male co-twins also show an elevated risk, but one that appears less pronounced. In contrast, news from other laboratories is more favorable for mothers of multiples. In 1989, researchers in Albany, New York demonstrated that mothers up to 55 years of age were less likely to develop breast cancer if their last delivery was a multiple birth.⁴ A 1997 study reported a similar protective effect from twin deliveries, but questioned whether this resistance was specific to final births.⁵ Several studies cited in these reports variously detected trends, albeit non-significant, toward both increased and decreased breast cancer risk among mothers of multiples. Differences in participants' age and/or family planning practices were thought to underlie some inconsistencies among studies.

Further investigation is warranted, but the findings so far raise many crucial questions: what factors unique to fraternal twinning might predispose fraternal female twins to breast cancer? What factors guarding against breast cancer do multiple pregnancies offer mothers? Are one or both sets of findings amplified in the event of higher order multiples? Do these findings apply equally to mothers conceiving naturally and those who do not? Given the rapid increases in fraternal twinning rates, a closer look at this research is warranted. Studies linking (1) breast cancer and fraternal female twinning and (2) reduced breast cancer frequency and bearing multiple birth children are summarized below.

Breast cancer and fraternal female twinning

The impetus for undertaking a study of breast cancer frequency in twins rested on the hypothesized association between breast cancer and in utero exposure to increased estrogen levels.³ The authors refer to several lines of research that guided their approach. It had already been demonstrated that maternal estrogen levels are twice as high in twin pregnancies, relative to non-twin pregnancies. It had also been shown that placental lactogen levels are higher in fraternal twin pregnancies than in identical twin pregnancies. (Lactogen stimulates progesterone production.) Furthermore, serum estrogen levels are higher in multiple birth mothers than in single birth mothers.

Another revealing finding is that levels of human chorionic gonadotropin (HCG) in cord blood and in maternal blood are highest when twin pregnancies include at least one female. Some previous breast cancer research suggested that the disease was elevated in twin populations, but none had organized the twin samples by zygosity. Thus, the investigators of this study reasoned that analyses of breast cancer with reference to twin-

ship, zygosity and sex would be an informative undertaking.

The sample included postmenopausal women chosen at random in the state of Iowa. Questionnaires were mailed at various intervals to identify women who were twins and singletons, and to obtain risk factor data including family history of breast cancer, reproductive history, alcohol use and use of hormone replacement therapy. Changes in health status were also tracked during the course of the study. Total mortality and breast cancer incidence data for 1986–1996 were obtained from the Iowa Cancer Registry and Iowa death certificates database. There were negligible differences between respondents and non-respondents in age, education, breast cancer risk factors, height, weight and other background variables.

The 538 twins who were identified represented 1.8% of the at-risk cohort of 29,197. Zygosity was determined by self-report in a 1992 follow-up questionnaire. Following adjustment for risk factors, twins showed a 1.7-fold increased risk of developing breast cancer, relative to non-twins. The elevated risk was, however, specific to fraternal twins (1.77), especially fraternal twins with twin sisters (2.14). These findings concur with some related results from previous twin research, with knowledge of hormonal–fetal relationships and with the suspected link between twinning and breast cancer. The data are compelling, given the large population-based sample, and likely to influence the future course of twin research on breast cancer risk. Depending on the final outcome, it may also affect health care practices of fraternal female twins who may be advised to seek more frequent medical examinations and preventative measures. Nevertheless, the authors wisely inserted some caveats into their interpretation. They noted, for example, that twinning is not a precise index of estrogen level and other factors (eg, older maternal age, known to be associated with

fraternal twinning⁶) may have affected the findings.

The self-report method of zygosity diagnosis may be more troubling than the investigators claim. They were aware of possible misdiagnoses (13% of the twins were uncertain of their twin type so were excluded from the study), but they suggested that errors would be random with respect to breast cancer status. That may or may not be true because some identical twins discordant for cancer could decide they are probably fraternal on that basis. A different zygosity-related issue was, however, not addressed: there is a well-known bias for twins and parents of twins to misclassify identical twins as fraternal.⁷ In contrast, misclassification of fraternal twins as identical occurs less frequently. If this situation occurred in the present study, it may have increased the number of at-risk 'fraternals', especially if disease discordance affected twin type assessment. Perhaps breast cancer risk is more similar in the two types of twin than the study suggested. Future studies of this type are advised to include questions from standard physical resemblance questionnaires that show over 90% agreement with serological studies.⁸ In fact, the investigators unknowingly included such two items – height and weight.

Breast cancer protection in mothers of multiples

A 1989 study conducted at the Albany Medical College in Albany, New York was the first to link multiple birth to reduced breast cancer risk in mothers.⁴ Participants were selected from the national Cancer and Steroid Hormone Study, conducted between 1960 and 1982. The sample included over 3,000 parous women between 20 and 54 years of age with newly diagnosed breast cancer, and over 4,000 controls from the same geographic location. Multiple births were reported among 118 cases and 181 controls. After adjusting for various reproductive variables, mothers whose multiples were last-born showed a 40% reduction in breast cancer risk. In contrast, mothers whose multiple births were followed by non-twin births failed to show resistance to the disease. Age at first multiple birth and years since most recent multiple birth were unrelated

to risk of breast cancer protection. The number of female infants in twin deliveries did not differ between cases and controls. Restricting analyses to women who conceived naturally did not alter the findings.

A 1997 study conducted by researchers from the Netherlands, England and Sweden extended this work using Swedish mothers of twins and singletons. Records of live-born infants and stillborns from 1961 to 1989 were used to define a cohort of women who delivered during this period. These women were then linked to the Swedish Cancer Registry to identify those who had developed breast cancer following delivery of their first child. Women born after 1939 who had delivered a child prior to cancer detection were identified as cases for the study. Randomly selected control subjects were then matched to these cases. After adjusting for parity and for age at first birth, mothers of twins showed a 29% risk reduction for breast cancer, relative to mothers of non-twins. In contrast with the 1989 study, the protective effect from a multiple birth delivery did not diminish following a singleton birth. The investigators noted, however, that the large confidence intervals surrounding the risk estimates prevented definitive conclusions on this point.

Reasons why mothers of multiples enjoy increased protection against breast cancer compared with non-twin mothers are speculative.⁴ The authors favor an explanation implicating the elevated levels of alpha-fetoprotein released by the fetal liver. This substance (derived from humans or from rodents) has been shown to block estrogen-stimulated growth of the rodent uterus and cause remission of estrogen-dependent breast cancer in rats. It was pointed out that intensity of exposure uniquely available from a twin pregnancy may be the key factor affording protection. This is because the actual levels of maternal hormonal exposure are equivalent in two singleton pregnancies and a twin pregnancy, yet there is no evidence of a cumulative protective effect from the former. Other details concerning the hormonal profiles of mothers of twins may offer additional explanations.⁵

This body of work is exciting for the insights it may shed on the biological correlates of twinning and on the etiology and prevention of breast can-

cer. An important line of inquiry will be determining if, and how, results vary in mothers bearing twins vs higher order multiples; studies so far have not made this distinction. Perhaps mothers of multiples will edge medical professionals closer to discovering new methods for preventing this devastating disease.

Twin processes and twin parenting

In vitro fertilization: single embryos

One day we may achieve the ultimate goal of one infant for every viable embryo generated in utero.⁹ Respect for the privacy of patient-physician relationships has prevented the United States from strictly regulating the number of embryos implanted in a woman's uterus as part of in vitro fertilization (IVF) procedures. Two or three embryos are typically transferred, although the number may be more. Hormonal treatments to induce ovulation may result in the release of multiple embryos and their subsequent fertilization, as in the case of the McCaughey septuplets. The physical, emotional and financial difficulties for caring for multiple premature infants and children are well-known.¹⁰ Resolution of this situation would involve the successful birth of a single healthy child following implantation of a single embryo. Dr Arthur Wisot, an infertility specialist from Reproductive Partners in California, and colleagues are researching the benefits of blastocyst embryos.¹¹ Blastocyst embryos mature until the 60–140 cell stage, as compared with typically implanted 16-cell embryos. These more mature embryos have a greater likelihood of survival and of yielding successful pregnancies and outcomes. The major advantage of this approach is that it can limit the number of embryos implanted, thus reducing the number of higher order multiple births. It should be noted that the author of the article from which this information was available referred to conceptions from simultaneously created embryos implanted at different times as 'triplets born several years apart'. Elsewhere, I have challenged the correctness of referring to such children as triplets, given their different intra-uterine environments and birth

cohorts.¹² Developing appropriate labels for novel kinships resulting from assisted reproductive technologies remains a worthwhile task.

Superfecundation: more puzzles

Findings surrounding superfecundation were given close attention in the last issue of *Twin Research*. Meanwhile, an especially intriguing case study appeared recently, adding to the interest and complexity of this phenomenon.¹³ A pregnant woman's premature contractions at 31 weeks necessitated ultrasonic study, revealing a diamniotic, monochorial placenta. Placental abruption at 33 weeks eventuated in the emergency delivery of two male infants, now aged 3 years and healthy. The single placenta, matching weights and sex of the twins was consistent with monozygosity, but this was not confirmed by serology nor by molecular genetic analysis. Blood group and DNA studies were later ordered by the court when, in the course of the parents' divorce proceedings, the father acknowledged uncertain paternity. Laboratory results revealed that the twins did not share a father.

The investigators speculated that the single placenta may have resulted from early fusion of separate placentae, an event occurring in approximately 40–50% of dizygotic twin births.^{14,15} The single chorion is more surprising because of its specific association with monozygotic twinning, yet discussion of this point was not provided. This would not be the first time non-identical twins were born with a single chorion – a 1981 report presented evidence consistent with polar body twinning, noting especially the monochorionicity of the pair in question.¹⁶ (Tests showed that the twins, a normal male and malformed female, resulted from fertilization of a mature ovum and a polar body. The authors noted that twinning thus occurred either at, or before, conception.) Events surrounding superfecundation should become clearer as technologies for managing multiple births and for determining paternity improve.

Twin parenting: natural vs two types of assisted conceptions

In vitro fertilization has enabled some infertile couples to bear children. (In

1995, IVF accounted for approximately 78% of live births resulting from reproductive assistance.¹⁷) Twins resulting from these conceptions pose specific emotional consequences for parents, especially mothers, that are now coming to light. Belgian researchers recently compared parenting stress and psychosocial well-being in 103 families with twins, organized into three groups:

- (1) couples conceiving twins naturally,
- (2) couples conceiving twins following mother's hormonal treatment and
- (3) couples conceiving twins by IVF.²⁰

Participants completed the Parenting Stress Index and General Health Questionnaire when their twin children were 10–13 months of age.

Overall, no significant differences were found among mothers and fathers in the three parent groups. However, some important differences among mothers emerged on some scales. In particular, first-time mothers conceiving twins through IVF or hormone treatment expressed greater stress related to parenting competence and health than mothers conceiving twins naturally. These mothers also indicated lower psychological well-being than new mothers who conceived naturally or previously infertile mothers who already had children. The investigators suggested that previously infertile mothers may entertain high expectations for their future child, partly associated with the waiting period and efforts invested in conceiving their child. The daily challenges of raising twins may later induce feelings of stress and inadequacy, thus challenging these notions. The need for specialized support for these first-time mothers of multiples is underlined by these results.

It is interesting to contrast these findings with other recent studies comparing parenting experiences among couples whose single children were conceived naturally, by adoption, by IVF, or by other assisted reproductive procedures. Studies in England¹⁹ and in the Netherlands²⁰ found that adoptive parents and parents whose children were not naturally conceived expressed somewhat greater satisfaction with their parent-

ing roles than parents whose children were naturally conceived. In contrast with the explanation given above, the authors suggested that time and expense invested in having these children may actually explain their parents' expressed pleasure. Of course, children in these families were not twins, thus easing child care responsibilities somewhat. Furthermore, these children were also older than those in the twin family study (2–8 years of age), so parents would have had more time to adjust to their new roles.

Continuing controversy: school placement, together vs apart?

Early in February 2000, I met mothers of twins in Pasadena, California. Common concerns united this parent group and similar groups I have met over the years, but one issue remains outstanding. Conflicts between parents and educators over whether to place twins in separate or common classrooms persist. Mandatory separation of twins at school is most often advised with a view towards fostering each twin's individuality and identity, but the time has come to rethink this practice. Separating twins who function well together could disrupt twins' evolving sense of self, thus having the opposite effect of what was intended. Researchers examining this situation systematically advocate forming school placement decisions on a case by case basis.^{21,22} Nevertheless, each fall, when the school term begins, the problem resurfaces as unhappy parents struggle to make correct choices for their children. Parents have indicated that school administrators are interested in reviewing the psychological literature on this topic. It is, therefore, important that researchers and multiple birth organizations make relevant research findings available.

School news is not completely discouraging, however. In 1993, the Oklahoma state legislature considered a resolution in which school districts would be asked to set placement policies allowing for separate review of each twin pair's situation. Dr Ramona Paul, the Oklahoma state assistant superintendent, commented, 'It's tradition that we do [separate twins in classrooms], but no one has ever studied it and asked, "Why".'²³ Twin researchers with interests in public

policy should consider closer involvement in decision-making by their local school system.

Twins' school placement policies undoubtedly vary within and between neighborhoods, cities and countries. Increased exchange of practices, outcomes and ideas would greatly assist twins, their families and their schools in addressing this question. A program now in place in England is likely to offer insights in the near future.²⁴

Multiple perspectives

Japanese researchers clone a cloned bull

In January 2000, scientists at the Kagoshima Prefectural Cattle Breeding Development Institute in Japan successfully cloned a cloned bull.²⁵ This was not the first time a clone had been cloned – in July, 1988, researchers at the University of Hawaii were able to clone cloned mice. The bull, however, was the largest animal to be duplicated in this way. The purpose behind the procedure was to make copies of high quality studs for producing beef quickly and in large quantities.

The researchers, as well as colleagues in the field, raised the possibility of premature aging in these cloned animals. Whether or not the cloned line of bulls will display early signs of aging has yet to be determined. This was also a concern with regard to Dolly, the famous Scottish lamb, yet early reports of accelerated aging were not confirmed.

First quadruplets of the millennium

Chaya Engel and her husband Rabbi David Engel, of Montreal, Canada, take credit for producing the first set of quadruplets of the new millennium.²⁶ (Final confirmation that this foursome was not preceded by another set elsewhere in the world is still pending. However, news of another set has not appeared since the birth was announced early this year.) The three boys and one girl were delivered by Cesarean section 11 weeks prior to term, and ranged in weight from 21b 8oz to 21b 15oz. Their mother, who had given birth previously to six other children, had taken medicine for menstrual regulation. The specific medication (unnamed) has been linked to

twin pregnancies, but not to higher order multiple births.

Multiple triplets

Healthy triplet daughters were delivered to Arcella Garcia, in Washington state, in early January 2000.²⁷ Triplet births do not usually become headlines, but this case was unusual for several reasons. Mrs Garcia was 54 years old at delivery, had already delivered eight children, had witnessed the birth of 13 grandchildren and had conceived her triplets naturally. She had terminated birth control treatments shortly before becoming pregnant, believing she would no longer conceive. Mrs Garcia, however, was upstaged several weeks later when 19-year-old Crystal Cornick, of Baltimore, delivered her second set of triplets.²⁸ Both of her triplet sets were also conceived naturally.

The birth of these unusual triplets and other higher order multiples is highly celebrated in the media and in people's private lives. However, these pregnancies pose high physical risks for mothers and infants and leave many children with developmental handicaps and delays. Two of the McCaughey septuplets born in November 1997 are showing physical disabilities, possibly cerebral palsy (CP).²⁹ Twins are more likely to be affected with CP than non-twins,³⁰ although only 40% of identical pairs are concordant.²

We hear less about unsuccessful higher order multiple births, yet they outnumber the successful ones. Possibly inspired by the birth of McCaughey septuplets, Ivette Zapa-Small of New Jersey, became pregnant with seven fetuses following fertility drug treatment.³¹ Her physician's suggestion to reduce the pregnancy to twins or triplets to improve her chance of a favorable outcome was rejected, due to conflict with her religious beliefs. In addition, she had recently lost a 21-month-old daughter from rheumatoid arthritis, so understandably found the concept of selective reduction distressing. (Psychological discomfort by prospective parents facing selective reduction decisions is not infrequent and has been documented in the medical literature.³²) Ultimately, all seven fetuses were spontaneously aborted, due to an infection. Cases like this reinforce the

critical goal of providing single children to infertile couples, see above.

Artists at work

I was visiting New York City in December 1999–January 2000 when I discovered that the ACA Galleries on East 57th Street, in Manhattan, was featuring a special event: an exhibition commemorating the 100th anniversary of the birth of identical twin painters, Moses (1899–1987) and Raphael Soyer (1899–1987).³³ The twins, born on Christmas Day in 1899, emigrated from Russia to the United States in 1913. The brothers each won numerous awards for their work and each had written and illustrated several books. Moses painted people's 'private moments', while Raphael tended towards 'complex configurations' of people and places – yet both were masters at capturing the moods and behaviors of their subjects. I was struck by the similar appearance of the multiple figures in many of their works, a probable legacy of their identical twinship.

Leafing through the Gallery Guide revealed another unexpected treasure: the exhibition 'Odd Nerdrum: Twins', on display around the corner.³⁴ Nerdrum, born in Norway in 1994, is considered the successor to Edvard Munch, famous for 'The Scream'. Nerdrum is the father of twins, but his artistic attention to twins preceded the birth of his daughters. The stark gallery held a small, but dazzling array of paintings depicting twins and mothers of twins. 'Twins at Dawn' shows infant twins resting peacefully side by side. The surrounding landscape appears dark and gloomy, but a bright light shines on the sleeping infants – the suggestion is innocence entering a less than innocent world. Other pictures show the twins' mother during pregnancy, while breastfeeding, and on an outing by the sea with the twins, gazing thoughtfully at them.

Japan's eldest twin passes away at 107 years

Centenarian twins, Kin Narita and Gin Kanie, were famous throughout Japan for their charm, candor and active life styles.³⁵ The two women, who lived in Nagoya, Japan, appeared to be identical – a photograph taken of the twins two years ago reveals matching faces, body postures and hand positions. Kin

passed away on 23 January 2000 at age 107, just two days after the twins attended a tree-planting ceremony in their country. She had 11 children, 11 grandchildren, 7 great-grandchildren and 1 great-great-grandchild. These data were not provided for her twin sister, but would be of interest to researchers studying genetic effects on child-bearing tendencies.

Kin ('Gold') and Gin ('Silver') hold the world's record for longevity in twins.³⁶ Thus, they are also a compelling example of links between genes and life-span expectancy. Genetic influences on longevity were revealed in a Danish twin study which estimated that 33% of life span differences were associated with genetic factors.³⁷

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