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Transgenerational effects of chemotherapy: Both male and female children born to women exposed to chemotherapy have fewer children

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ABSTRACT

Background: There is little known about the transgenerational effect of chemotherapy. For example, chemotherapy is known to decrease fecundity in women. But if women are able to have offspring after chemotherapy exposure, do these children also have decreased fecundity?

Methods: This study is a retrospective cohort study utilizing the Utah Population Database (UPDB), a comprehensive resource that links birth, medical, death and cancer records for individuals in the state of Utah. The male and female children (F1 generation) of chemotherapy-exposed women (F0 generation) were identified. The number of live births (F2 generation) to this F1 generation was compared to two sets of chemotherapy-unexposed, matched controls using conditional Poisson regression models (regression coefficient, 95% confidence interval, P-value). The first unexposed was established using the general population and the second unexposed was established using first cousins to the F1 generation.

Results: The exposed F1 individuals had 77.2% fewer children (−1.48; −2.51 to −0.70; p = 0.001) relative to the unexposed general population. F1 males had 86.9% fewer children (−2.03; −4.91 to −0.51; p = 0.005) and F1 females had 70.5% fewer children (−1.22; −2.40 to −0.36; p = 0.016). When comparing to their unexposed cousins, the F1 generation (both sexes combined) had 74.3% (−1.36; −2.82 to −0.29; p = 0.029) fewer children.

Conclusion: The sons and daughters (F1 generation) of chemotherapy-exposed women have fewer live births when compared to both matched, unexposed general population and cousin controls. Chemotherapy may have a transgenerational effect in exposed women which needs further investigation.

1. Introduction

Advances in healthcare have greatly improved outcomes for women battling cancer. Almost 65% of people with malignancies will live at least five years after diagnosis and the survival from pediatric or young adult cancers may be approaching 80% [1]. Survivors are now able to live many additional years which may not have been previously possible [2–4]. This has led to new areas of research including the study of cancer survivors and the challenges they face. Studies have shown that survivors are at increased risk of psychosocial difficulties, infertility, hospitalizations, early menopause and mental health problems [5–11]. Very little, however, is known about the transgenerational consequences of surviving cancer. Specifically, what risks occur to offspring who were conceived after their parents were exposed to chemotherapy?

Chemotherapeutic agents have revolutionized cancer treatment and improved survival. They are loosely grouped into categories by their mechanisms of action (alkylating agents, anti-metabolites, anti-microtubules, etc.) but they all may fundamentally alter DNA sequences and gene expression, potentially perturbing normal epigenetic mechanisms [12–15]. These genetic changes are more profoundly seen in germ cells potentially allowing alterations to be transmitted to offspring with unknown clinical consequences [16–19]. The limited research available has focused on animals in controlled experimental settings. One mouse study showed significant genomic instability down to three subsequent generations from exposure to chemotherapeutic agents

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cyclophosphamide, mitomycin C and procarbazine.15] It is problematic to translate these studies to humans. More compelling and robust epidemiological studies are needed. The transgenerational effects of chemotherapy in humans are almost entirely unknown and of increasing concern given the improved survival rates [20,21].

Utilizing the unique clinical and informatics resources available at our institution - a state-wide, generational population database - we tested whether the progeny of female cancer survivors were indeed at risk for adverse health outcomes in relation to the offspring of unexposed individuals. Our hypothesis is that both male and female children (F1 generation) of chemotherapy-exposed females (F0 generation) have fewer offspring (F2 generation) relative to unexposed comparison groups.

2. Materials and methods

This study was approved by the Institutional Review Board of the University of Utah by the Utah Resource for Genetic and Epidemiological Research. This is a retrospective cohort study utilizing the Utah Population Database (UPDB), a comprehensive population-based resource that links birth, medical, death and cancer records for individuals in Utah, a state with a population of 3 million. Health information is derived from medical records from the two largest health care systems in the state. Birth, death, marriage and divorce certificates and state driver's license data provide further information regarding demographics and health diagnoses. Cancer data is available through linked information from the Utah Cancer Registry (UCR), an original member of the National Cancer Institute Surveillance, Epidemiology and End Results (SEER) network of cancer registries, which captures statewide cancer incidence data dating back to 1966; it became a member of SEER in 1973.

Three generations families identified in UPDB serve as the basis for the analyses. The exposed generation (F0) was identified first using UCR data starting from 1966. Eligible F0 women are those who were diagnosed with cancer anytime from birth to age 45, treated with chemotherapy, and able to conceive after exposure to chemotherapeutic agents. Chemotherapy exposure is also recorded as an event, however, the type and dosage of chemotherapy is not available. Only those in the F0 generation with all children (F1s) above the age of 15 (reproductive-age) before the study end date (December 31st, 2015) were included for analysis. All eligible F1s were conceived after chemotherapy exposure in the F0 generation. There were no other exclusion criteria. There were 132 women in the exposed F0 group who met all the inclusion criteria and who gave birth to 132 children (exposed F1), who were all over 15 years of age at the time of the data collection.

The fecundity (defined as number of offspring) of this exposed F1 generation was compared with two sets of controls. The first control was drawn from a general population cohort using a 10:1 unexposed-to-exposed ratio matching on both F0 and F1 birth year and gender. The second control group consisted of unexposed first cousins of the exposed F1 individuals matched by birth year (+/− 5 years). Eligible unexposed first cousins were identified as the children (F1) of siblings of the exposed F0 generation who did not have cancer and were not exposed to chemotherapy (Fig. 1). For example, there were 132 exposed F0 females who had 97 unexposed siblings. These siblings (F0 generation) had 146 children, which serve as our F1 cousin control cohort.

Conditional Poisson regression models (regression coefficient, 95% confidence interval, P-value) were used to compare the number of live births in the exposed F1 generation to each of the two unexposed F1 groups. These regression models controlled for F0 maternal marital status at the time of F1 births to control socioeconomic factors [22–24]. The percentage change in the number of offspring between the exposed and unexposed cohorts is calculated by taking the natural exponent of the regression coefficient and then subtracting from one. The analysis was performed for all F1s combined and then stratified by gender and repeated. The P-value level of significance was set at ≤ 0.05.

3. Results

Selected demographic characteristics including gender and average age are listed in Table 1. There were 132 F1 individuals in the exposed group with a mean age of 19 years at the time of this data collection. There were 59 females and 73 males in this group. The unexposed general population was matched based on a 10:1 ratio and had 1278 individuals averaging 19-years of age. There were 146 unexposed first cousins of the exposed group that were available for the study averaging 21 years of age.

The distribution of cancer type of the F0 generation is listed in Table 2. The number of offspring in the exposed F1 generation and general population cohort are also listed in Table 2. Lymphoma (39.4%), breast cancer (17.4%) and leukemia (14.4%) were the most prevalent cancers. The overall number of offspring for all three cohorts is listed in Table 3. Only five individuals (3.8%) in the exposed F1 group have offspring whereas 10% of the unexposed general population and 15.1% of the unexposed first cousins have offspring. Both the general population and first cousin cohorts have individuals with multiple offspring. No individuals in the exposed cohort have more than one offspring.

The exposed F1 individuals have 77.2% fewer overall children (-1.48; -2.51 to -0.70; $p = 0.001$) relative to the unexposed general population. When stratified by gender, the 73 F1 males have 86.9% fewer children (-2.03; -4.91 to -0.51; $p = 0.005$) and the 59 F1 females have 70.5% fewer children (-1.22; -2.40 to -0.36; $p = 0.016$). When compared to their unexposed first cousins, the F1 generation have 74.3% (-1.36; -2.82 to -0.29; $p = 0.029$) fewer children.

4. Discussion

Our results agree with our hypothesis and suggest that both male and female offspring of female cancer survivors treated with chemotherapy have lower rates of fecundity compared to controls. To the best of our knowledge, there have been no prior studies examining this relationship. Less than 4% of individuals in the F1 exposed group have children, compared to 10% and 15% in the unexposed general population and first cousin cohorts, respectively. When we stratify the exposed F1 group, male F1s had even fewer live births compared to female F1s. Most likely, this is an artifact from both the low sample size and young age of the F1s, and no further conclusions should be drawn at this time.

There is limited research regarding how chemotherapy can affect families across generations. Proposed mechanisms of action include direct toxicity and epigenetic perturbations on germ cells. These mechanisms could not be directly tested in this study because of its archival and retrospective nature but are hypothesized from evidence in animal and laboratory studies described above [12–16,19].

Women, unlike men, are also born with a fixed supply of germ cells that do not undergo cyclic regeneration. They are inherently more susceptible to environmental toxins and passing potentially damaged or altered DNA to their children [25,26]. Chemotherapeutic agents have wide-ranging effects on germ cells. For example, they increase the level of reactive oxygen species (ROS) which directly damages DNA, alters expression of transcription factors, modifies gene expression and disturbs proper oocyte maturation [27]. This increased oxidative stress also reduces blood flow for germ cells. Hypoxic conditions can potentially change epigenetic modification patterns, such as DNA methylation and histone acetylation, which are then transmitted to offspring [28].

Several other findings are noteworthy. Approximately 78% (11,858/15,261) of F0 women who had children never had children again after being diagnosed with cancer. Most of these women were