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# Maternal use of personal care products during pregnancy and risk of testicular germ cell tumors in sons

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ABSTRACT

*Background:* The etiology of testicular germ cell tumors (TGCT) is poorly understood, however, exposure to endocrine disrupting chemicals (EDCs) may be related to increased risk. Personal care products, some of which contain EDCs, are widely used on a daily basis and are known to cross the placenta, be present in breastmilk, and are capable of inducing reproductive tract abnormalities. To determine the association between personal care product use during pregnancy and breastfeeding and TGCT risk, an analysis among mothers of TGCT cases and controls was conducted.

*Methods:* The US Servicemen's Testicular Tumor Environmental and Endocrine Determinants (STEED) study enrolled TGCT cases and controls and their mothers between 2002 and 2005. The current analysis examined personal care product use during pregnancy among 527 mothers of TGCT cases and 562 mothers of controls. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated using unconditional logistic regression adjusting for identified covariates.

*Results:* Maternal use of face lotion more than one time per week was associated with a significantly increased risk of TGCT (OR: 1.42, 95% CI: 1.08–1.86, p-trend: 0.01). None of the other products examined (perfume, hairspray, nail polish, hair dye, permanent wave, body lotion, deodorant, sunscreen) were associated with TGCT risk.

*Conclusions:* Frequent exposure to face lotion during pregnancy and while breastfeeding may be associated with increased TGCT risk. Further investigation into the endocrine disrupting effects of personal care products is warranted.

## 1. Introduction

With an incidence rate of approximately 8 per 100,000 (Ghazarian et al., 2017), testicular germ cell tumors (TGCT) are rare tumors in the general population, but are the most commonly occurring cancer among men between the ages of 15 and 44 years in the United States (US) (McGlynn and Cook, 2009). The etiology of TGCT is poorly understood; the only well-described risk factors include cryptorchidism, prior history of TGCT, family history of TGCT, and increased adult stature (McGlynn, 2001). The positive association of cryptorchidism with TGCT, as well as the similarity between primordial germ cells and testicular germ cell neoplasia in situ (formerly called carcinoma in situ) suggests that TGCT may be determined very early in life and may have a hormonal etiology (Dieckmann and Pichlmeier, 2004; Skakkebaek et al., 1987; Toppari and Kaleva, 1999; Rajpert-De Meyts et al., 2003; Toppari et al., 2006). The ability of some environmental chemicals to act as estrogens and anti-androgens has led to the hypothesis that endocrine disrupting chemicals (EDCs) may be associated with the risk of TGCT and other male reproductive disorders (cryptorchidism, hypospadias, and impaired spermatogenesis) which together comprise the Testicular Dysgensis Syndrome (TDS) (Toppari et al., 1996; Skakkebaek et al., 2001).

Commonly used personal care products are known to contain EDCs such as phthalates, bisphenol A (BPA), perfluorinated chemicals, triclosan, and parabens (Witorsch and Thomas, 2010; Koniecki et al., 2011). Many personal care products are applied directly to the body allowing EDCs to be absorbed through the skin and to reach the circulatory system. Personal care product use is much more common

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among women than men (Biesterbos et al., 2013), and the fetuses of pregnant women may be especially vulnerable to the risks of EDCs. EDCs are able to cross the placenta (Gundacker et al., 2016) and may adversely affect placental functioning and/or fetal development. Postnatally, infant exposure may occur via breastfeeding as EDCs have been found in breastmilk (Stefanidou et al., 2009) and have been reported to affect endogenous reproductive hormones (Main et al., 2006). EDCs can transfer by passive diffusion from the blood stream into the mammary alveolar gland where they then can become incorporated into breastmilk at concentrations which are comparable to other fatty parts of the body (Stefanidou et al., 2009).

EDCs have been shown to have estrogenic and/or anti-androgenic effects (Schug et al., 2016; Gore et al., 2015). It has been suggested that that exposure to EDCs during gestation could result in reproductive tract abnormalities in the fetus and TGCT later in life through a relative excess of estrogen (Sharpe and Skakkebaek, 1993). Furthermore, exposure to EDCs in postnatal life through breastmilk may interfere with germ cell development (Main et al., 2006). To determine the association between maternal personal care product use during pregnancy and TGCT risk, we conducted an analysis among mothers of cases and controls in The US Servicemen's Testicular Tumor Environmental and Endocrine Determinants (STEED) study.

## 2. Methods

A detailed description of the STEED study has been reported previously (McGlynn et al., 2007). In brief, between April 2002 and January 2005, men between the ages of 18–45 years who had at least one serum sample stored in the US Department of Defense Serum Repository (DoDSR, Silver Spring, MD, USA) were eligible to participate in the study. The DoDSR has been storing serum samples from military personnel since 1985. A person-specific identifier is used in the DoDSR database to link the serum samples to the Defense Medical Surveillance System (DMSS) (Rubertone and Brundage, 2002) and to other military medical databases to determine which military personnel develop medical conditions. Men who developed TGCT while on active duty were eligible to participate as cases whereas men who did not develop TGCT were eligible to participate as controls. Diagnoses of TGCT were limited to classic seminoma or nonseminoma (embryonal carcinoma, yolk sac carcinoma, choriocarcinoma, teratoma, mixed germ cell tumor), as spermatocytic tumors (formerly known as spermatocytic seminomas) are thought to be etiologically distinct from other TGCTs. The diagnoses were based on the original pathology reports or on review of the pathology slides.

The STEED study was designed as a matched case-control study. Eligible controls were individually matched to cases on the following factors: age at diagnosis (within 1 year), race (white, black, other), and date when serum was donated (within 30 days). Each participant was asked for permission to contact his mother to enroll her in the study. A total of 1247 mothers were contacted: 43 were found to be ineligible, 28 were incompletely enrolled at study completion, and 16 could not be located. Of the 1160 eligible mothers contacted, 72 refused to participate. Overall, 527 case mothers and 562 control mothers were completely enrolled in the study. Participating mothers were interviewed by a female interviewer over the telephone. Supervising interviewers listened in, at random, to the interviews, to assure that the interviews were conducted in a similar fashion across all the mothers.

The computer-assisted telephone interview was composed of nine modules. Select questions from the demographic history and personal care product use sections were used for the present analysis. Mothers of both cases and controls were asked to report on use and the frequency of use for the following personal care products during their pregnancy and while they breastfed: perfume, hairspray, nail polish, hair dye, perm/relaxer, face lotion, body lotion, deodorant/antiperspirant, and sunscreen. The study was approved by the institutional review boards of the National Cancer Institute (Bethesda, MD, USA) and the Walter Reed Army Institute of Research (Silver Spring, MD, USA).

### 2.1. Statistical analysis

Frequency of personal care product use was categorized into usage groups (never, ≤ once/week, > once/week). Cohen's kappa statistic was calculated to measure the agreement between frequency of exposures to each personal care product category during pregnancy and exposures while breastfeeding, which showed moderate to very good agreement of frequency of personal care product use during pregnancy and breastfeeding. Thus, duration of exposure was simply calculated as the duration of pregnancy plus the duration of breastfeeding in weeks.

Adjusted odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association between the exposures and TGCT risk in sons. Mothers who didn't complete a questionnaire were not included in the study. As the mothers themselves were not matched to one another, unmatched analyses were performed using unconditional logistic regression. Risk estimates were initially minimally adjusted,

**Table 1.**
Distribution of characteristics among study participants, The STEED Study, 2002–2005.

| | Mothers of sons with TGCT (Cases) (n = 527) mean (sd) | Mother of sons without TGCT (Controls) (n = 562) mean (sd) | |
|---|---|---|---|
| Mother's age at son's birth (yrs) | 24.0 (5.1) | 24.3 (4.9) | |
| Son's age at TGCT diagnosis (yrs) | 27.1 (5.7) | 27.1 (5.7) | |
| Maternal weight gain during pregnancy (lbs.) | 29.7 (14.1) | 28.6 (13.3) | |
| | n (%) | n (%) | p-value |
| Mother's age at son's birth (yrs) | | | 0.10 |
| < 20 | 118 (23.2) | 89 (16.4) | |
| 20–29 | 314 (61.7) | 375 (69.2) | |
| ≥30 | 77 (15.1) | 78 (14.4) | |
| Son's age at TGCT diagnosis (yrs) | | | 0.91 |
| < 20 | 26 (4.9) | 22 (3.9) | |
| 20–24 | 176 (33.4) | 197 (35.1) | |
| 25–29 | 166 (31.5) | 170 (30.3) | |
| 30–34 | 85 (16.1) | 99 (17.6) | |
| 35–39 | 57 (10.8) | 56 (10.0) | |
| ≥40 | 17 (3.2) | 18 (3.2) | |
| Race | | | 0.64 |
| White | 467 (88.6) | 504 (89.7) | |
| Black | 12 (2.3) | 15 (2.7) | |
| Other | 48 (9.1) | 43 (7.7) | |
| Breastfed son | | | 0.02 |
| Yes | 170 (32.3) | 148 (26.3) | |
| No | 357 (67.7) | 414 (73.7) | |
| Number of Products Used | | | 0.92 |
| 0 | 19 (3.6) | 15 (2.7) | |
| 1 | 40 (7.6) | 46 (8.2) | |
| 2 | 84 (15.9) | 97 (17.3) | |
| 3 | 108 (20.5) | 128 (22.8) | |
| 4 | 118 (22.4) | 114 (20.3) | |
| 5 | 88 (16.7) | 84 (14.9) | |
| 6 | 41 (7.8) | 49 (8.7) | |
| 7 | 23 (4.4) | 23 (4.1) | |
| 8 | 5 (0.9 | 4 (0.7) | |
| 9 | 1 (0.2) | 2 (0.4) | |
| Maternal weight gain during pregnancy (lbs.) | | | 0.21 |
| < 20 | 159 (32.9) | 168 (32.0) | |
| 20–24 | 80 (16.6) | 104 (19.8) | |
| 25–34 | 113 (23.4) | 136 (25.9) | |
| ≥35 | 131 (27.1) | 117 (22.3) | |

Abbreviations: SD = Standard Deviation.