Published in final edited form as:

Alcohol. 2009 May ; 43(3): 241–245. doi:10.1016/j.alcohol.2008.12.002.

Maternal Smoking, Alcohol, and Coffee Use during Pregnancy and Son's Risk of Testicular Cancer

Morgana L. Mongraw-Chaffin*, Barbara A. Cohn*, Andrew T. Anglemeyer*, Richard D. Cohen*, and Roberta E. Christianson*

*Child Health and Development Studies, Center for Research on Women's and Children's Health, Public Health Institute. 1683 Shattuck Avenue, Ste.B., Berkeley, CA 94709

Abstract

It has been suggested that increased risk for testicular cancer occurring worldwide may be due to exposures during fetal development. Lifestyle or environmental exposures may be the most important predictors of risk. However, few studies have directly examined these exposures prospectively. The Child Health and Development Studies is a 40-year follow-up of 20,530 pregnancies occurring between 1959 and 1967. There were 20 cases of testicular cancer diagnosed through 2003 among sons with a maternal interview in early pregnancy. Cases were matched to three controls on birth year and race. Odds ratios and 95% confidence intervals were calculated with exact conditional logistic regression. Compared to controls, mothers of testicular cancer cases were more likely to drink alcohol (unadjusted odds ratio = 3.2, 95% confidence interval: 0.83, 15.48 for above versus below the median for controls) and less likely to drink coffee (unadjusted odds ratio = 0.19, 95% confidence interval: 0.02, 1.02 for above versus below the median). Case mothers were neither more nor less likely to smoke. While low power may limit interpretation of negative results, the prospective design minimizes bias. In this cohort, maternal serum testosterone in pregnancy was previously reported to be lower in women who drank alcohol. Since populations with high testicular cancer risk also have lower maternal testosterone, we suggest that testosterone could play a role in explaining the higher risk of son's testicular cancer among mothers who drank alcohol during pregnancy.

Keywords

Testicular Cancer; Alcohol; Coffee; Smoking; Pregnancy; Prospective

Introduction

It has been suggested that increased risk for testicular cancer occurring worldwide (Bray et al., 2006; Huyghe et al., 2003; Maffezzini, 2007; Purdue et al., 2005; Richiardi et al., 2004) may be due to exposures during fetal development. (Bergstrom et al., 1996; Ekbom, 1997; Jacobsen et al., 2006; Maffezzini, 2007) Lifestyle or environmental exposures may be the most important predictors of risk. (Hemminki and Li, 2002) However, few studies have

© 2013 Elsevier Inc. All rights reserved

Corresponding author: Barbara A. Cohn Child Health and Development Studies, Center for Research on Women's and Children's Health, Public Health Institute. 1683 Shattuck Avenue, Ste.B., Berkeley, CA 94709 bcohn@chdstudies.org; Phone: 510-649-6390 Fax: 510-842-0747.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final citable form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

directly examined these exposures. We are aware of seven studies that examined maternal behavior during pregnancy and son's testicular cancer and only one is prospective (Pettersson et al., 2007) (See Supplemental Tables). Moreover, while these seven prior studies examined smoking, other correlated maternal behaviors have rarely been examined. Only two studies that we are aware of, both retrospective, have investigated maternal drinking during pregnancy and son's testicular cancer (Brown et al., 1986; Weir et al., 2000) and none to our knowledge investigated maternal coffee consumption. We present new results on prenatal risk factors for testicular cancer from the Child Health and Development Studies (CHDS), a 40-year follow-up of 20,530 pregnancies enrolled before birth.

Materials and Methods

CHDS subjects were members of the Kaiser Permanente Health Plan, residing in the Oakland California Area. (van den Berg et al., 1988) Nearly all eligible pregnancies occurring between 1959 and 1967 were enrolled. Women were interviewed in early pregnancy about their use of tobacco, alcohol, and coffee.

Germ cell testicular (ICD No. C62) cancer cases were identified by linking study records to data in the California Cancer Registry through 2003. One CHDS son was diagnosed with embryonal carcinoma in infancy (ICD No. M9070/3), and he was not included in this analysis. Twenty-three CHDS sons (born 1959–1967) were diagnosed with testicular cancer in adulthood (age range of 17 to 38 years). Median age at diagnosis was 32 and only one case was cryptorchid. Sixteen cases were Caucasian, two were Asian, one was Hispanic, and one was multiracial. Thirteen cases were seminomas, and 10 were non-seminomas. Cases lacking maternal interview data were excluded (N=3). For each of the remaining 20 cases, three controls, known to be free of testicular cancer and to reside in the California Cancer Registry surveillance area on the date of diagnosis of the case, were matched to the case on race and year of birth. Observations were censored when lost to follow-up due to death or residence outside of the surveillance areas for the California Cancer Registry, as previously described. (Cohn et al., 2001; Cohn et al., 2007) Controls were selected at random from the pool of matches if more than three were available. All subjects gave informed consent and the Institutional Review Board of the Public Health Institute approved the protocols for this study.

Associations between risk factors and case/control status were analyzed using the Wilcoxon Rank Sum Test of differences within matching groups and exact conditional logistic regression. Due to the computational limitations of the exact method and to limit stratification of the small sample but preserve the ability to mutually adjust potential confounders, dichotomized risk variables were used: mother's cigarette smoking, mother's alcohol consumption, mother's coffee consumption, number of prior births, mother's body mass index, son's birth weight, and length of gestation were all dichotomized at the median value for controls (0 = less than median for controls, 1 = at or above median for controls). All analyses were performed using version 9.1 of SAS and LogXact 7 Procs for SAS. (Cytel Statistical Software and Services)

Results

Based on Wilcoxon Ranked Sum Tests, the most notable differences between cases and controls were higher maternal alcohol consumption and lower maternal coffee consumption during pregnancy and shorter gestations (Table1).

Based on exact conditional logistic regression, mothers who drank more alcohol were more likely to have a case offspring, and this effect became larger when adjusted for most other

variables (Table 2). Mothers who drank more coffee were less likely to have a case offspring than those who drank less than the median coffee consumption.

Discussion

A particular strength of this study is that the women were interviewed before widespread knowledge that maternal smoking and drinking could lead to negative health outcomes for their offspring. (1981; Jones and Smith, 1973; Office of the Surgeon General, 1980) The stigmatization of alcohol use during pregnancy presents methodological challenges for studies conducted later. The large confidence intervals for the effect estimates reflect the small sample size (Table 2). Although CHDS is a large pregnancy cohort, the small number of testicular cancer cases is expected even among 9,744 liveborn sons. However, the prospective nature of the study and evidence that self-reported maternal behaviors during pregnancy are particularly accurate in our cohort (English et al., 1994) indicate a low level of bias. Low power to detect a modest association is a possible explanation of null results for other variables examined.

Two previous case-control studies of the relationship between maternal drinking and testicular cancer are not definitive. (Brown et al., 1986; Weir et al., 2000) The study with negative findings reported rates of alcohol drinking among case mothers in the 1990's that were less than 50 percent of those reported in the mothers of cases in the present study who were interviewed between 1959 and 1967. (Weir et al., 2000) The study reporting a positive association interviewed women earlier, between 1979 and 1981, and adjusted for prenatal smoking. (Brown et al., 1986) Both prior studies interviewed women after their sons had been diagnosed.

One indication that our cohort is similar to other study populations previously investigated is that we observe the same lack of association between son's testicular cancer and prenatal smoking (Table 2). (Brown et al., 1986; Coupland et al., 2004; Henderson et al., 1979; McGlynn et al., 2006; Pettersson et al., 2007; Swerdlow et al., 1987; Weir et al., 2000)

We have previously reported that maternal caffeine consumption during pregnancy may increase the risk of son's cryptorchidism in the CHDS cohort. (Mongraw-Chaffin et al., 2008) This caffeine effect is primarily due to coffee use and the effect holds when coffee alone is considered. In this article we report that maternal coffee consumption may decrease the risk of testicular cancer. This contradiction indicates the need for more intense investigation into the relationship between cryptorchidism and testicular cancer within a given population.

We have previously reported that alcohol consumption is associated with lower maternal testosterone levels in pregnancy. (Stevens et al., 2005) Since populations with high testicular cancer risk also have lower maternal testosterone, (Zhang et al., 2005) we suggest that testosterone could play a role in the maternal alcohol association observed. Fetal exposure to ethanol may affect hormonal or testicular development in humans (Westney et al., 1991) and in rats, specifically by disrupting the fetal testosterone surge. (Blanchard and Hannigan, 1994; Li and Kim, 2003; McGivern et al., 1998; Ward et al., 2003; Ward et al., 2002) As drinking trends in women of child-bearing age and pregnant women continue to remain high in the US (Centers for Disease Control and Prevention, 1997; Centers for Disease Control and Prevention, 2002; Crome and Kumar, 2007; Ebrahim et al., 1998) and Europe, (Andersen AM et al., 2001; Crome and Kumar, 2007) this association, if replicated, has the potential to play a large role in the cancer incidence of young men.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

Funding for this study was provided by The National Institute of Health (N01 DK63422) and The Lance Armstrong Foundation. The study sponsors had no role in study design, collection, analysis, or interpretation of the data, the writing of the report, or the decision to submit the paper for publication.

References

- Surgeon general's advisory on alcohol and pregnancy. Food and Drug Administration Drug Bulletin. 1981; 11:9–10.
- Andersen AM, Olsen J, Gronbaek MN. Did the changed guidelines on alcohol and pregnancy by the National Board of Health and Welfare change alcohol consumption of pregnant women? Ugeskr Laeger. 2001; 163:1561–1565. [PubMed: 11268810]
- Bergstrom R, Adami H-O, Mohner M, Zatonski W, Storm H, Ekblom A, Tretli S, Teppo L, Akre O, Hakulinen T. Increase in Testicular Cancer Incidence in Six European Countries: a Birth Cohort Phenomenon. J. Natl. Cancer Inst. 1996; 88:727–733. [PubMed: 8637026]
- Blanchard BA, Hannigan JH. Prenatal ethanol exposure: effects on androgen and nonandrogen dependent behaviors and on gonadal development in male rats. Neurotoxicol. Teratol. 1994; 16:31–39. [PubMed: 8183187]
- Bray F, Richiardi L, Ekblom A, Pukkala E, Cuninkova M, Moller H. Trends in testicular cancer incidence and mortality in 22 European countries: continuing increases in incidence and declines in mortality. Int. J. Cancer. 2006; 118:3099–3111. [PubMed: 16395710]
- Brown LM, Potters LM, Hoover RN. Prenatal and Perinatal Risk Factors for Testicular Cancer. Cancer Res. 1986; 46:4812–4816. [PubMed: 3731127]
- Centers for Disease Control and Prevention. Alcohol consumption among pregnant and childbearing-aged women -- United States, 1991 and 1995. Morbidity and Mortality Weekly Report. 1997; 46:346–350. [PubMed: 9148136]
- Centers for Disease Control and Prevention. Alcohol use among women of childbearing age --United States, 1991–1999. Morbidity and Mortality Weekly Report. 2002; 51:273–276. [PubMed: 11952279]
- Cohn BA, Cirillo PM, Christianson RE, van den Berg BJ, Siiteri PK. Placental characteristics and reduced risk of maternal breast cancer. J. Natl. Cancer Inst. 2001; 93:1133–1140. [PubMed: 11481384]
- Cohn BA, Wolff MS, Cirillo P, Sholtz RI. DDT and Breast Cancer in Young Women: New Data on the Significance of Age at Exposure. Environmental Health Perspectives. 2007; 115:1406–1414. [PubMed: 17938728]
- Coupland CA, Forman D, Chilvers CE, Davey G, Pike MC, Oliver RT. Maternal risk factors for testicular cancer: a population-based case-control study (UK). Cancer Causes Control. 2004; 15:277–283. [PubMed: 15090722]
- Crome IB, Kumar MT. Epidemiology of drug and alcohol use in young women. Seminars in Fetal and Neonatal Medicine. 2007; 12:98–105. [PubMed: 17292681]
- Cytel Statistical Software and Services. LogXact 7 Procs for SAS Users. Cytel Inc.; Cambridge Mass:
- Ebrahim SH, Luman ET, Floyd RL, Murphy CC, Bennett EM, Boyle CA. Alcohol consumption by pregnant women in the United States during 1988–1995. Obstet. Gynecol. 1998; 92:187–192. [PubMed: 9699749]
- Ekblom A. Growing evidence that several human cancers may originate in utero. Semin Cancer Biol. 1997; 8:237–244. [PubMed: 9870030]
- English PB, Eskenazi B, Christianson RE. Black-white differences in serum cotinine levels among pregnant women and subsequent effects on infant birthweight. Am. J. Public Health. 1994; 84:1439–1443. [PubMed: 8092368]

- Hemminki K, Li X. Cancer risks in Nordic immigrants and their offspring in Sweden. *Eur. J. Cancer Prev.* 2002; 38:2428–2434.
- Henderson B, Benton B, Jing J, Yu M. Risk factors for cancer of the testis in young men. *Int. J. Cancer.* 1979; 23:598–602. [PubMed: 37169]
- Huyghe E, Matsuda T, Thonneau P. Increasing incidence of testicular cancer worldwide: a review. *J. Urol.* 2003; 170:5–11. [PubMed: 12796635]
- Jacobsen R, Moller H, Thoresen SO, Pukkala E, Kjaer SK, Johansen C. Trends in testicular cancer incidence in the Nordic countries, focusing on the recent decrease in Denmark. *Int. J. Andrology.* 2006; 29:199–204.
- Jones KL, Smith DW. Recognition of the fetal alcohol syndrome in early infancy. *Lancet.* 1973; 2:999–1001. [PubMed: 4127281]
- Li H, Kim KH. Effects of Ethanol on Embryonic and Neonatal Rat Testes in Organ Cultures. *J. Androl.* 2003; 24:653–660. [PubMed: 12954654]
- Maffezzini M. TC Incidence Increasing: Spread the Word. *Eur Urol.* 2007; 51:596–597. [PubMed: 16973261]
- McGivern RF, Handa RJ, Raum WJ. Ethanol exposure during the last week of gestation in the rat: inhibition of the prenatal testosterone surge in males without long-term alterations in sex behavior. *Neurotoxicol. Teratol.* 1998; 20:483–490. [PubMed: 9697975]
- McGlynn KA, Zhang Y, Sakoda LC, Rubertone MV, Erickson RL, Graubard BI. Maternal smoking and testicular germ cell tumors. *Cancer Epidemiol. Biomarkers Prev.* 2006; 15:1820–1824. [PubMed: 17035387]
- Mongraw-Chaffin ML, Cohn BA, Cohen RD, Christianson RE. Maternal Smoking, Alcohol Consumption, and Caffeine Consumption during Pregnancy in Relation to a Son's Risk of Persistent Cryptorchidism: A Prospective Study in the Child Health and Development Studies Cohort, 1959–1967. *Am. J. Epidemiol.* 2008; 167:257–261. [PubMed: 18024986]
- Office of the Surgeon General, U. S. P. H. S.. The Health Consequences of Smoking for Women: A Report of the Surgeon General. Public Health Service. Office of the Surgeon General; United States: 1980.
- Pettersson A, Akre O, Richiardi L, Ekblom A, Kaijser M. Maternal smoking and the epidemic of testicular cancer-A nested case-control study. *Int. J. Cancer.* 2007; 120:2044–2046. [PubMed: 17278105]
- Purdue MP, Devesa SS, Sigurdson AJ, McGlynn KA. International patterns and trends in testis cancer incidence. *Int. J. Cancer.* 2005; 115:822–827. [PubMed: 15704170]
- Richiardi L, Bellocco R, Adami HO, Torrang A, Barlow L, Hakulinen T, Rahu M, Stengrevics A, Storm H, Tretli S, et al. Testicular cancer incidence in eight northern European countries: secular and recent trends. *Cancer Epidemiol. Biomarkers Prev.* 2004; 13:2157–2166. [PubMed: 15598775]
- Stevens RG, Cohen RD, Terry MB, Lasley BL, Siiteri P, Cohn BA. Alcohol consumption and serum hormone levels during pregnancy. *Alcohol.* 2005; 36:47–53. [PubMed: 16257353]
- Swerdlow AJ, Huttly SR, Smith PG. Prenatal and familial associations of testicular cancer. *Br. J. Cancer.* 1987; 55:571–577. [PubMed: 3606949]
- van den Berg BJ, Christianson RE, Oechsli FW. The California Child Health and Development Studies of the School of Public Health, University of California at Berkeley. *Paediatr. Perinat. Epidemiol.* 1988; 2:265–282. [PubMed: 3070486]
- Ward IL, Ward OB, Affuso JD, Long WD 3rd, French JA, Hendricks SE. Fetal testosterone surge: specific modulations induced in male rats by maternal stress and/or alcohol consumption. *Horm. Behav.* 2003; 43:531–539. [PubMed: 12799169]
- Ward OB, Ward IL, Denning JH, French JA, Hendricks SE. Postparturitional testosterone surge in male offspring of rats stressed and/or fed ethanol during late pregnancy. *Horm. Behav.* 2002; 41:229–235. [PubMed: 11855908]
- Weir HK, Marrett LD, Kreiger N, Darlington GA, Sugar L. Pre-natal and peri-natal exposures and risk of testicular germ-cell cancer. *Int. J. Cancer.* 2000; 87:438–443. [PubMed: 10897052]

- Westney L, Bruney R, Ross B, Clark JF, Rajguru S, Ahluwalia B. Evidence that gonadal hormone levels in amniotic fluid are decreased in males born to alcohol users in humans. *Alcohol*. 1991; 26:403–407.
- Zhang Y, Graubard BI, Klebanoff MA, Ronckers C, Stanczyk FZ, Longnecker MP, McGlynn KA. Maternal hormone levels among populations at high and low risk of testicular germ cell cancer. *Br. J. Cancer*. 2005; 92:1787–1793. [PubMed: 15841083]

Table 1

Distribution of prenatal risk variables among testicular cancer cases and controls in the Child Health and Development Studies 1959–2003

Characteristics	Cases			Controls			Difference within Matching Group Case - Mean of 3 Controls*		
	Median	Interquartile Range	N**	Median	Interquartile Range	N**	Mean of Differences	Standard Error	p-value for Matched Wilcoxon Signed Rank Test for Cases vs. Controls
Mother's Alcohol Consumption (Drinks per Week)	0.6	1.6	17	0.0	0.8	52	0.28	0.15	0.09
Mother's Cigarette Smoking (Cigarettes per Day)	4.75	24.5	18	7.0	17	58	0.01	0.13	0.94
Mother's Coffee Consumption (Cups per Day)	1.0	5.0	17	2.0	3.0	50	−0.27	0.13	0.07
Mother's Body Mass Index (kg/m ²)	21.4	2.7	18	21.7	3.3	60	−0.09	0.12	0.49
Mother's Age (Years)	25	7.5	20	26	11	60	−0.08	0.13	0.59
Parity (Number of Prior Births)	1	1.5	20	1	1.5	60	−0.28	0.33	0.57
Son's Length of Gestation (Days)	279.5	13	20	285	13.5	60	−0.3	0.12	0.03
Son's Birth Weight (kg) [†]	3.39	0.65	20	3.42	0.84	60	−0.07	0.14	0.83

* Mean difference, standard error, and p-value are for variables coded as above or below the median for controls.

** Number of cases and controls differ due to missing data on some characteristics.

[†] Only four sons were low birth weight (< 2500 grams) and none were very low birth weight (<1500 grams). Of the low birth weight sons, one was a case and three were controls making the low birth weight rate 5% for both cases and controls.

TABLE 2

Association of prenatal characteristics with testicular cancer estimated by exact conditional logistic regression, * in the Child Health and Development Studies from 1959–2003

	<u>Odds Ratio</u>	<u>95% Confidence Interval</u>
Univariate Models		
Mother's Alcohol (1 / 0 drinks per week)	3.24	0.83, 15.48
Mother's Smoking (7/<7 cigarettes per day)	1.06	0.26, 3.89
Mother's Coffee (2/<2 cups per day)	0.19	0.02, 1.02
Mother's BMI (21.7/ <21.7 kg/m ²)	0.69	0.20, 2.32
Mother's Age (26/<26 years)	0.72	0.22, 2.23
Parity (1/ 0 prior births)	1.00	0.24, 3.57
Son's Length of Gestation (285/<285 days)	0.25	0.04, 0.93
Son's Birth Weight (3.4/ <3.4 kg)	0.78	0.24, 2.31
Mutually Adjusted Bivariate Models		
Mother's Alcohol (1 / 0 drinks per week)	5.69	1.07, 59.23
Mother's Coffee (2/<2 cups per day)	0.13	0.01, 0.81
Mother's Alcohol (1 / 0 drinks per week)	4.01	0.94, 24.04
Mother's BMI (21.7/ <21.7 kg/m ²)	0.90	0.23, 3.54
Multivariate Model		
Mother's Alcohol (1 / 0 drinks per week)	5.83	1.11, 59.14
Mother's Coffee (2/<2 cups per day)	0.15	0.01, 0.94
Mother's BMI (21.7/ <21.7 kg/m ²)	0.69	0.12, 3.60

* All models were run with binary variables using contrasts of below and above the median for controls. All models were based on subjects with non-missing values for the variables of interest (sample sizes shown in Table 1).