Prenatal and Perinatal Risk Factors for Testicular Cancer

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ABSTRACT

In an attempt to determine the risk factors responsible for the dramatic increases in testicular cancer incidence in young adults, mothers of testicular cancer cases and controls were questioned about in utero exposures, pregnancy-related conditions, and perinatal factors during their pregnancies with the 202 cases and the 206 controls. The strongest risk factor was low birth weight with a greater than 12-fold risk (confidence interval = 2.8 to 78.1) for subjects weighing 5 lb or less at birth compared to those who weighed over 5 lb. A statistically significant 2-fold increase in risk was associated with unusual bleeding or spotting during pregnancy, regardless of whether medication was taken for this condition. Other exposures during pregnancy associated with a statistically significant increase in risk were: use of "sedatives"; alcohol consumption; and exposure to X-rays. No excess risk was associated with the use of hormones during pregnancy. The findings for birth weight and abnormal uterine bleeding suggest that significant compromise of the normal maternal-fetal environment may be associated with subsequent increase in risk of testicular cancer. However, this increase in risk is not great enough to explain the dramatic increases in testicular cancer that have occurred in young adults.

INTRODUCTION

The incidence of testicular cancer in the United States has been increasing dramatically for young adult men, aged 15 to 44 yr (1). Because these men were relatively young when their cancer was diagnosed, it has been speculated that pre- and perinatal factors may play a role in the etiology of young adult testicular cancer (2). This paper presents the results of a case-control study of testicular cancer in which the biological mothers were questioned about in utero exposures, pregnancy-related conditions, and perinatal factors during their pregnancies with the cases and controls.

MATERIALS AND METHODS

The potential study population consisted of the living biological mothers of 271 testicular cancer cases (88% of the cases identified) and 259 cancer controls (90% of the controls identified) who participated in an interview study during 1979 to 1981. The controls were patients at the same hospital as the cases and were similar in age to the cases (±2 yr of age). Study subjects were 18 to 42 yr old at the time of cancer diagnosis. Since the RR was adjusted for hospital and variables of interest was the RR approximated by the odd ratio (4).

Summary RR estimates adjusted for the variables birth weight in pounds (<=6.0, 6.1 to 8.0, >8.0), number of packs of cigarettes smoked per day (none, <1, >=1), and number of drinks of alcoholic beverages per week (<=1, 1, >2) were obtained by maximum likelihood procedures (5) with 95% CI as described by Gart (6). These same procedures were used to adjust for the stratifying (matching) variables: hospital and age at diagnosis. Since the RRs adjusted for hospital and age at diagnosis were similar to the unadjusted RRs, RRs adjusted for these two factors are not presented in this paper. t tests were used to test case-control differences in mean birth weight and parental ages at study subject's birth (7). Mantel's extension test (8) was used to test for trends (2-tailed) in risk related to alcohol and cigarette consumption. The Pearson product moment correlations (9) were used to measure the closeness of a linear relationship between birth weight in lb (<=5.0, 5.1 to 6.0, 6.1 to 7.0, 7.1 to 8.0, 8.1 to 9.0, >9.0), number of packs of cigarettes smoked per day (none, <1, >=1), and number of drinks of alcoholic beverages per wk (<=1, 1, >2). A logistic model (10) was used to simultaneously assess the effects of these three factors on the probability of being a case. $\chi^2$ tests of homogeneity were used to test for case-control differences in referral patterns (12).

RESULTS

Ninety-six % of the case mothers and 97% of the control mothers were White with the remainder either Black, Hispanic, Asian, or American Indian. A history of undescended testis was reported for 10% of the cases and 3% of the controls (RR = 3.4, CI = 1.3 to 8.8), based on a positive report by either the son or the mother. Many of the specific maternal factors under investigation (e.g., birth weight, gestational age, and hormone use) have been associated with the development of undescended testis or cryptorchidism (13, 14). Therefore, in order to eliminate the potential for confounding of these factors by a history of undescended testis, only data for the 202 cases and the 206 controls without a history of undescended testis were analyzed.

The mean age at diagnosis was 26 yr for both the testicular cancer cases and their controls. The percentage of study subjects seen at each hospital was: NIHCC, 51%; USUNH, 22%; and WRAMC, 27%. There were no significant differences in the geographical distribution between cases and controls ($\chi^2 = 6.6; P = 0.25$), minimizing the possibility of referral bias. The diagnoses among the controls were as follows: Hodgkins disease (27%); non-Hodgkins lymphoma (19%); melanoma (17%); soft tissue sarcoma (8%); leukemia (8%); bone tumors (7%); nervous system tumors (4%); and other cancers (10%).

The mean ages of the mother (26.7 yr for cases, 26.5 yr for controls; $P = 0.745$) and the father (28.6 yr for cases, 29.0 yr for controls; $P = 0.401$) at the study subject's birth were similar for cases and controls. No substantial differences in RR were seen for study subjects (a) delivered vaginally head first (184 cases, 190 controls), (b) delivered breech (6 cases, 9 controls), (c) who were twins (5 cases, 4 controls), and (d) who were firstborn children (62 cases, 66 controls). Also, there was no

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2 The abbreviations used are: NIHCC, NIH Clinical Center; USUNH, Uniformed Services University, Naval Hospital; WRAMC, Uniformed Services University, Walter Reed Army Medical Center; RR(s), relative risk(s); CI, confidence interval.
difference in the percentage of cases and controls born with birth defects (4%). An elevated risk (RR = 1.7, CI = 0.5 to 6.0) was associated with Cesarean deliveries, although this finding was based on 9 cases and 5 controls.

The birth weight of the sons as reported by the mothers ranged from 3.1 to 13.4 lb. Mean birth weight was significantly lower for the cases (7.3 lb) than for the controls (7.6 lb), \( P = 0.014 \). The RRs of testicular cancer according to birth weight are presented in Table 1. The RR for birth weights of 5 lb or less, 13.5, was significantly elevated when compared to birth weights of the referent category of 7.1 to 8.0 lb. RRs seen for birth weights of 5.1 to 6.0 lb and for greater than 8 lb were all less than 1.5 and were not significantly different from one. When birth weight was dichotomized into 5 lb or less and greater than 5 lb, cases were 12.5 times more likely to have low birth weight than controls (CI = 2.8 to 78.1). This RR remained similar after adjustment by mothers' age in years at the time of the sons' births (<24, 24 to 28, ≥28), mothers' level of education (≤11th grade, high school, > high school), whether or not the study subject was a twin, and whether or not delivery was by Cesarean section.

The risk of testicular cancer according to reported months of gestation was also examined. A RR of 1.5 (CI = 0.8 to 2.8) was seen for those born in 7 to 8 mo compared to those born in 9 to 10 mo. Since birth weight and gestational age are highly correlated, months of gestation was examined stratified by birth weight (Table 2). Relative to the heaviest sons with the longest gestation, the greatest risk was seen for sons of low birth weight delivered during the seventh or eighth mo, although the risk was also elevated for low-birth-weight sons delivered at 9 to 10 mo. No excess risk has been seen for sons of birth weight greater than 5 lb delivered at 7 to 8 mo.

Mothers were asked about their consumption of cigarettes and alcohol during pregnancy. Cigarette smoking during the index pregnancy was reported by 31.0% of the mothers (median, 10 cigarettes) with consumption ranging from 1 to 40 cigarettes per day. The RR for testicular cancer associated with ever versus never smoking during pregnancy was 1.3 (CI = 0.8 to 2.0). The 20.3% of the mothers who drank at least one drink of alcoholic beverages per wk reported consuming between 1 and 14 drinks per wk with a median of one drink. Case mothers were more likely to have at least one drink per wk during pregnancy than were control mothers (RR = 1.6, CI = 1.0 to 2.7).

Smoking and drinking were significantly correlated with each other for both cases (\( r = 0.32, P < 0.01 \)) and controls (\( r = 0.16, P = 0.02 \)), but neither smoking nor drinking was significantly correlated with birth weight in the controls, and only smoking was significantly correlated with birth weight in the cases (\( r = -0.22, P < 0.01 \)). Presented are the RRs for smoking and drinking adjusted for each other. Compared to nonsmokers, there was no excess risk for smoking more than one pack a day (RR = 0.8, CI = 0.4 to 1.5), but the risk for smoking one pack or less a day was 1.5 (CI = 0.8 to 2.9). Although consuming one drink per wk during pregnancy was not strongly related to testicular cancer, case mothers were twice as likely to have two or more drinks per wk than control mothers. The RRs were 1.1 (CI = 0.6 to 2.2) and 2.3 (CI = 1.0 to 5.2), respectively, for mothers who consumed one drink and more than one drink per wk. These same patterns of risk for smoking and drinking were seen within each birth weight category. The smoking-adjusted RRs according to a finer categorization of alcohol intake (0, 1, 2, 3 or 4, ≥5 drinks per wk) did not show a significant increasing trend in RRs with amount of alcohol consumed (\( P \) for trend = 0.14). When a binary logistic model was used to simultaneously control for smoking, drinking, and birth weight, the RRs were not altered substantially.

Mothers were asked whether they had experienced excessive nausea or vomiting, toxemia, or unusual bleeding or spotting during their pregnancy with the study subject and whether they took any medication to treat these conditions. These results are presented in Table 3. Although the RR for having toxemia was elevated (but not significant), the RR for mothers who reported taking medication for toxemia was not elevated. There was a slight nonsignificant risk associated with nausea or vomiting. The RR was significantly elevated for mothers who reported unusual bleeding (RR = 2.4) and was elevated regardless of whether or not they took medication. The majority of mothers who took bleeding medication began taking it during the second or third mo of pregnancy. Only 2 (both case mothers) of the 19 mothers who reported using a medication for bleeding mentioned a specific hormone by name. The types of medication reported were: pills of unknown type (7 case mothers, 4 control mothers); shots of unknown type (3 case mothers, 2 control mothers); and vaginal cream (1 case mother). The risks were

Table 1. Relative risks for testicular cancer according to sons' birth weight

<table>
<thead>
<tr>
<th>Birth wt (lb)</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;5</td>
<td>22</td>
<td>2</td>
<td>13.5</td>
<td>2.9–86.6</td>
</tr>
<tr>
<td>5.1–6.0</td>
<td>18</td>
<td>18</td>
<td>1.2</td>
<td>0.5–2.7</td>
</tr>
<tr>
<td>6.1–7.0</td>
<td>38</td>
<td>50</td>
<td>0.9</td>
<td>0.5–1.7</td>
</tr>
<tr>
<td>7.1–8.0</td>
<td>58</td>
<td>71</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>8.1–9.0</td>
<td>42</td>
<td>44</td>
<td>1.2</td>
<td>0.7–2.1</td>
</tr>
<tr>
<td>≥9.0</td>
<td>19</td>
<td>16</td>
<td>1.5</td>
<td>0.6–3.3</td>
</tr>
</tbody>
</table>

* Excludes 5 cases and 5 controls with unknown birth weight.

Table 2. Relative risks for testicular cancer according to sons' birth weight and months of gestation

<table>
<thead>
<tr>
<th>Birth wt</th>
<th>No. of gestation</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;5 lb</td>
<td>9 or 10</td>
<td>159</td>
<td>179</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td></td>
<td>7 or 8</td>
<td>12</td>
<td>19</td>
<td>0.7</td>
<td>0.3–1.6</td>
</tr>
<tr>
<td>≤5 lb</td>
<td>9 or 10</td>
<td>7</td>
<td>1</td>
<td>7.9</td>
<td>1.0–172.3</td>
</tr>
<tr>
<td></td>
<td>7 or 8</td>
<td>15</td>
<td>1</td>
<td>16.9</td>
<td>2.3–346.7</td>
</tr>
</tbody>
</table>

* Excludes 5 cases and 5 controls with unknown birth weight and 4 cases and 1 control with unknown mo of gestation.

Table 3. Relative risks for testicular cancer according to conditions experienced during pregnancy

<table>
<thead>
<tr>
<th>Condition</th>
<th>No. of cases</th>
<th>No. of controls</th>
<th>RR</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Toxemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had condition</td>
<td>No 186</td>
<td>197</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Used medication</td>
<td>No 11</td>
<td>4</td>
<td>2.9</td>
<td>0.8–11.1</td>
</tr>
<tr>
<td></td>
<td>Yes 3 4</td>
<td>0.8</td>
<td>0.1–4.3</td>
<td></td>
</tr>
<tr>
<td>Excessive nausea/vomiting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had condition</td>
<td>No 142</td>
<td>151</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Used medication</td>
<td>No 35</td>
<td>33</td>
<td>1.1</td>
<td>0.6–2.0</td>
</tr>
<tr>
<td></td>
<td>Yes 21 19</td>
<td>1.2</td>
<td>0.6–2.4</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DK</td>
<td>3</td>
<td>3.2</td>
<td>0.3–80.5</td>
</tr>
<tr>
<td>Unusual bleeding/spotting</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Had condition</td>
<td>No 173</td>
<td>193</td>
<td>1.0</td>
<td></td>
</tr>
<tr>
<td>Used medication</td>
<td>No 14</td>
<td>7</td>
<td>2.2</td>
<td>0.8–6.3</td>
</tr>
<tr>
<td></td>
<td>Yes 13 6</td>
<td>2.4</td>
<td>0.8–7.3</td>
<td></td>
</tr>
<tr>
<td></td>
<td>DK</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
</tbody>
</table>

* Excludes "don’t know" responses to each condition.

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nonsignificantly elevated for unusual bleeding in pregnancies resulting in a live birth other than the index pregnancy (RR = 1.3) and for mothers who had ever had a miscarriage or a stillbirth (RR = 1.1).

The risk of treated nausea was examined according to whether the study subject was a firstborn child, because positive results had been reported in a previous study (2). Among the firstborn study subjects, case mothers were 2.3 times more likely to have been treated for nausea (CI = 0.7 to 7.9). Similar to the finding for nausea, the risk associated with unusual bleeding or spotting for sons who were the firstborn child (RR = 3.6, CI = 0.8 to 17.6) was higher than the risk for sons born later (RR = 2.3, CI = 1.0 to 5.5).

The following questions were asked to obtain information on the use of female hormones during pregnancy: (a) did your physician determine you were pregnant by administering pills or shots to see if you would have a menstrual period? (b) do you recall ever taking diethylstilbestrol (DES), estrogen, progesterone, or any other female hormone? (c) do you recall ever taking other medications to prevent a miscarriage? Including the two mothers who reported taking hormones as a medication for bleeding, a total of four cases (2.0%) and five control (2.4%) mothers (RR = 0.8, CI = 0.2 to 3.5) reported taking exogenous hormones during the index pregnancy. The types of hormones received were: diethylstilbestrol (2 case mothers, 2 control mothers); estrogen (1 control mother); progesterone (1 case mother); progesterone pregnancy test (1 case mother); a hormone pregnancy test, type not specified (1 control mother); and a hormone shot, type not specified (1 control mother).

Mothers were also asked whether they ever took any of the following types of medication during their pregnancy: (a) medication for high blood pressure; (b) prescribed pain killers; (c) sedatives, tranquilizers, or sleeping pills; (d) stimulants or amphetamines; and (e) thyroid medication. A general question about any other medications used was also asked, and the names of each were recorded. The reasons for taking these medications were not ascertained. The medications identified from the general question were assigned to either one of the five drug categories mentioned above or to drug families (15) based on therapeutic characteristics. Table 4 presents the results for the five drug categories and for the two drug families reported by five or more mothers, antibiotics and vitamins/minerals. The RRs were not elevated for the two most common medications, painkillers (analgesics) and vitamins/minerals. RRs were nonsignificantly elevated for high blood pressure medicine and stimulants, but they were significantly elevated (RR = 2.9) for a more inclusive “sedative” category. Drug families included in the “sedative” category were sedatives, antitussives, antihistamines, and tranquilizers. The individual RRs for these drug families were 1.6, 4.3, 2.2, and 2.7, respectively, compared to nonusers of “sedatives.” Two mothers reported taking a type of sedative but did not specify the name or type; and one case mother reported taking dexamethasone as a sedative, although this medication is actually a stimulant. Adjustment for birth weight did not substantially change the RRs associated with the use of any medication.

Mothers were also questioned about exposure to X-rays received during their pregnancy. When abdominal X-rays were stratified by birth weight, the RRs were similar for each category of birth weight, ranging from 2.0 to 3.2. Table 5 presents the RRs for prenatal X-rays and adjusted for sons’ birth weight. There were significant risks associated with receiving any type of X-ray (RR = 2.3) and for receiving X-rays to the abdomen/pelvis (RR = 2.7). Nonsignificant excess risks were seen for those receiving chest or dental X-rays. Most of the X-rays to the abdomen/pelvis occurred during the third trimester (16 cases, 7 controls) and were used to determine the position or size of the baby. Third trimester dental (2 cases, 1 control) and chest X-rays (1 case, 1 control) were reported infrequently.

DISCUSSION

For some time, there has been speculation that the marked peak of testicular cancer incidence in young adults might be due to pre- or perinatal risk factors. The profound increases in incidence over time for young adult males (1) suggest that an environmental factor that has similarly varied over time might be responsible. Given the magnitude of this increase one would expect that this factor should have been identified by analytical epidemiological studies. However, to date the factor(s) responsible for these dramatic increases remains elusive.

The strongest risk factor for testicular cancer in this study of patients without a history of cryptorchidism was low birth weight. Specifically, those subjects weighing 5 lb or less at birth experienced a 12-fold increase in risk compared to those who weighed over 5 lb. The association was with low birth weight per se, as there was no consistent pattern of risk for birth weights above 5 lb. Because of the high degree of correlation of birth weight with gestational age, it was not entirely possible to separate the effects of these two variables. However, low birth weight appeared to be the more important variable when independent effects were assessed.

A further evaluation of low birth weight revealed that 12.4% of the cases and 3.6% of the controls who were single births of known birth weight weighed 2500 g or less. The percentage of low-birth-weight controls is similar to that calculated for all single live born United States White males in 1950 less than or equal to 2500 g, 4.6%, after adjusting for a 20% infant mortality rate (16, 17).

It is noteworthy that one recent study of testicular cancer observed a 3-fold increased RR associated with a birth weight of less than 6 lb (2), and another study described an excess risk associated with premature delivery (18). In addition, analysis of a prospective study of over 50,000 pregnancies identified a 3-fold risk of cryptorchidism and a 4-fold increase of inguinal

<table>
<thead>
<tr>
<th>Table 4</th>
<th>Relative risks for testicular cancer according to type of medication taken by the mother during pregnancy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of medication used</td>
<td>No. of cases</td>
</tr>
<tr>
<td>High blood pressure medication</td>
<td>7</td>
</tr>
<tr>
<td>Pain killers</td>
<td>19</td>
</tr>
<tr>
<td>&quot;Sedatives&quot;</td>
<td>16</td>
</tr>
<tr>
<td>Stimulants</td>
<td>2</td>
</tr>
<tr>
<td>Thyroid medication</td>
<td>2</td>
</tr>
<tr>
<td>Antibiotics</td>
<td>5</td>
</tr>
<tr>
<td>Vitamins/minerals</td>
<td>53</td>
</tr>
</tbody>
</table>

* Each risk relative to 1.0 for nonusers of each medication.

<table>
<thead>
<tr>
<th>Table 5</th>
<th>Relative risks for testicular cancer according to prenatal exposure to X-rays adjusted for birth weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of X-ray</td>
<td>No. of cases</td>
</tr>
<tr>
<td>None</td>
<td>168</td>
</tr>
<tr>
<td>Any</td>
<td>34</td>
</tr>
<tr>
<td>Abdomen/pelvis</td>
<td>20</td>
</tr>
<tr>
<td>Chest</td>
<td>8</td>
</tr>
<tr>
<td>Dental only</td>
<td>6</td>
</tr>
</tbody>
</table>

* Excludes 3 controls who did not know whether they had X-rays. |

<table>
<thead>
<tr>
<th>Table 6</th>
<th>Relative risks for testicular cancer according to prenatal exposure to X-rays adjusted for birth weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Type of X-ray</td>
<td>No. of cases</td>
</tr>
<tr>
<td>None</td>
<td>168</td>
</tr>
<tr>
<td>Any</td>
<td>34</td>
</tr>
<tr>
<td>Abdomen/pelvis</td>
<td>20</td>
</tr>
<tr>
<td>Chest</td>
<td>8</td>
</tr>
<tr>
<td>Dental only</td>
<td>6</td>
</tr>
</tbody>
</table>

* Excludes 3 controls who did not know whether they had X-rays. | Excludes 1 case who did not know whether the fetus was exposed to X-rays. | One case also had a dental X-ray.
hernia in childhood associated with low birth weight (13). The
strength and consistency of the association of low birth weight
or premature delivery with testicular cancer and with two of the
major risk factors for testicular cancer suggest that these rela-
tionships may provide substantial clues to the etiology of testic-
ular cancer. It will be of particular importance to determine
whether low birth weight and testicular cancer share common
risk factors, or whether low birth weight (or its correlates) is
itself a risk factor.

The two studies of testicular cancer previously referred to (2,
18) suggested that a variety of factors possibly responsible for
increased estrogenic exposure during pregnancy were risk fac-
tors for testicular cancer in young men. These factors included:
exogenous hormone exposure during the first trimester, includ-
ing hormonal pregnancy tests; and nausea of pregnancy severe
enough to require treatment, particularly when it was the wom-
an’s first pregnancy. No excess use of hormones during preg-
nancy by the mothers of the cases was observed in this study.
However, only seven mothers reported exposure to specific
hormones, and only two reported having a hormonal pregnancy
test.

Since so few case and control mothers were able to specify
the specific type of medication taken for bleeding during preg-
nancy, it is probable that the number of mothers who reported
hormone use during pregnancy is an underestimate. However,
the percentage of control mothers who reported the use of
diethylstilbestrol and other hormones during pregnancy (2.4%)
was similar to findings reported by Schottenfeld et al. (19) for
his hospital controls (2.5%) and Depue et al. (2) (1.9%). Since
a considerably smaller percentage of our case mothers reported
hormone use (2.0%) compared to results published by Schot-
tenfeld et al. (5.8%) and Depue et al. (7.3%), it is possible that
the inability to recall the type of drug taken for bleeding and
spotting may have resulted in a biased risk estimate for hormone
use.

However, this study did find a statistically significant 2-fold
increase in risk associated with unusual bleeding or spotting
during the index pregnancy, regardless of whether medication
was taken for this condition. This finding supports the hypo-
thesis of an altered hormonal milieu within the mother being a
risk factor for testicular cancer (2), although the type of alter-
ation is unclear. Since a history of abnormal bleeding in other
pregnancies and a history of miscarriage were only slightly
more common among the case mothers, the alteration appears
to be pregnancy specific, rather than a more pervasive hormonal
disorder of the mother.

The risk of testicular cancer was only slightly increased for
treated or untreated nausea. Among firstborn subjects whose
mothers were treated for nausea, the RR rose to 2.3. While not
significant and less than the 4-fold risk previously reported (2),
this lends some support to the previous findings.

Three other statistically significant associations that emerged
from the analysis of exposures during pregnancy were: use of
“sedatives”; exposure to X-rays during pregnancy; and alcohol
consumption. However, these associations are difficult to in-
terpret because the findings lack specificity or do not exhibit
a clear dose response. Also, these associations could be due to
chance, since a variety of pregnancy exposures were explored.
Specifically, the category “sedatives” contained a variety of
different chemical compounds, and the risk associated with
the category was not due to any particular compound. The highest
risk for X-ray exposure was observed for X-rays of the abdomen
and pelvis; however, there were 2-fold excess risks for proce-
dures involving little or no X-ray exposure to the fetus, such as
chest films and dental X-rays. To date, human studies of
radiation and testicular cancer have not suggested an associa-
tion (20), although some experimental evidence supports the
possibility that testicular tumors could be radiogenic (21, 22).
While RRs were elevated for consumers of two or more drinks
of alcoholic beverage per wk, a statistically significant trend in
risk was not seen when the number of drinks drunk per wk was
broken into finer categories. Also, the high correlation between
smoking and drinking makes it impossible to tell which factor
is driving the association, even though no consistent relation-
ship with amount smoked was apparent for the risk of testicular
cancer.

Information about a variety of other exposures during preg-
nancy was collected in an attempt to uncover previously unident-
dified risk factors. It was reassuring that the two major types
of medication consumed during pregnancy, analgesics and vi-
tamin/mineral preparations, were unassociated with risk of
testicular cancer.

As in any investigation, associations or the failure to find
associations could also be due to bias. Response rates were
high, minimizing the opportunity for bias due to nonresponse.
The nature of the control group also raises the possibility of
another type of bias. It is possible that some of the pre- or
perinatal exposures studied could play an etiological role in a
substantial proportion of all cancers in young adults. While we
think this unlikely, if this were the case, it is possible that an
important association of interest could have been “matched
out” since the comparison group was composed of young men
with other cancers. However, the choice of other cancers for
the comparison population was purposeful since pregnancy-
related variables may be especially subject to recall bias. Because
the case and control mothers were both being queried about
exposures during pregnancy to sons who subsequently devel-
oped a malignancy, recall bias should not be an issue. Also,
since the controls chosen had similar referral patterns as the
cases, selection bias should not be a factor.

This study found a number of pre- and perinatal factors
related to testicular cancer, although none of these associations
appears to be responsible for the marked age and time patterns
in the descriptive epidemiology of this tumor. The finding of
an elevated risk for low birth weight suggests that continued
exposure to the normal intrauterine environment in the later
stages of pregnancy conveys substantial protection against the
development of testicular cancer. In addition, the excess risk
found for unusual bleeding or spotting also suggests that alter-
ation of this normal maternal-fetal environment results in an
excess risk of testicular cancer. Whether the causal alterations
involve changes in estrogen levels as previously suggested (2)
or some other hormonal or nonhormonal factor remains to be
clarified. While the risks found for “sedatives,” alcohol con-
sumption, and X-ray exposure were not as consistent as those
for birth weight and bleeding, the strength of the associations
noted and/or the prevalence of these exposures in the general
population warrant further investigation. Hopefully, the find-
ings presented from this study may provide useful leads for
other investigators studying the etiology of testicular cancer.

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Prenatal and Perinatal Risk Factors for Testicular Cancer

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