Testicular Cancer and Hormonally Active Agents

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Abstract

Testicular cancer is a rare cancer, with an age-adjusted incidence of 3.8/100,000 in Canada. This disease accounts for 1.1% of all malignant neoplasms in Canadian males. Despite the low overall incidence of testicular cancer, it is the most common malignancy among young men, 25-34 years old. The incidence rate of testicular cancer has been increasing since the middle of the 20th century in many western countries, including Canada, the United States, the Nordic Countries, and Britain. The increasing trend in testicular cancer rates has been particularly noticeable in eastern European countries such as Slovenia. Countries with a sufficient long period of cancer registration, such as Denmark, document this trend back to the first half of the 20th century.

The etiology of testicular cancer is not well understood. Most of the established risk factors are related to *in utero* events including: cryptochidism, carcinoma *in situ*, and exposure to estrogen *in utero*. These established risk factors suggest that hormonal exposures may affect testicular cancer risk, and that endocrine toxicants may play a role in the induction of this lesion. However, the types of hormonally active environmental chemicals, the pathways in which they act, and their associated risk cancer remain unknown. Currently, there is a lack of direct evidence regarding the link between endocrine toxicants and testicular cancer risk. As well, the association between estrogenic or anti-androgenic compounds and testicular cancer has not yet been examined in an analytical epidemiologic study.

Introduction

Several common human cancers including testis, breast, and prostate cancer may share a similar mechanism of carcinogenesis, in which both endogenous and exogenous hormones affect cell proliferation. Exposure to such agents increases the opportunity for the accumulation of random genetic errors[1]. Although testicular cancer incidence may be influenced by exposures to endocrine toxicants, the extent of which such agents may play a role in the induction of testicular cancer is unclear at this time. Epidemiological studies have not found a strong link between hormones and testicular cancer. The few known related risk factors for testicular cancer include cryptochidism[2-17], and *in utero* exposure to estrogen[3;16;18], while late onset of puberty has a protective effect[5;8;14;19-21]. These risk factors appear to be linked by their relation to hormone exposure in both the pre and postnatal period, suggesting a possible link between testicular cancer and endocrine modulating substances.

1) Epidemiology

The International Agency for Research on Cancer (IARC) recognizes four specific types of testicular tumours: seminomas, embryonal carcinomas, malignant teratomas and choriocarcinomas[22]. These can be combined into two histological categories: seminomas and non-seminomas; a more detailed histology appears to have little relevance in research or clinical settings[23]. Approximately 50% of all germ cell tumours are seminomas and the remaining 50% are non-seminomas[24]. Various co-factors are required to stimulate these stem cells to develop into different types of testicular tumours[25].

In most countries testicular cancer is rare, with an age-standardized incidence rate ranging from about 1/100,000 in Asian and African/African-American populations, to 9.2/100,000 in Denmark[26]. The age distribution of testicular cancer is distinct from that for other

cancers, with the majority of cases occurring between the ages of 25-35[27]. A second, much smaller, peak occurs after 80 years of age[27-29]. Testicular cancer incidence varies markedly by race, with blacks and other non-white races exhibiting extremely low rates in comparison with white populations[30].

Since the middle of the 20th century the incidence of testicular cancer has been increasing in many western countries, including Canada[27], the United States[28], the Nordic Countries[31], and England[32]. In the last 40 years the worldwide incidence of testicular cancer has doubled[33]. In Canada, a 50% increase in the incidence rate of testicular cancer has been observed over the last 25 years[27]. Since 1970, the incidence rate has increased about 60% overall in Ontario, representing an increase of 2% per annum[34]. Testicular cancer accounts for 1.1% of all malignant neoplasms in Canadian males; and as it occurs primarily in young males, it represents an important source of morbidity for this age group[27]. Mortality rates are very low and the five-year survival rate has increased during the last 30 years from about 63% to over 90%[35]

The potential role of hormones and environmental exposures influencing testicular cancer is demonstrated in Norwegian males that were born during the Nazi Occupation (1940-1944). This cohort experienced a decreased risk of testicular cancer in comparison with those born in the five year time periods before or after this period (1935-39 and 1945-1949)[29]. A similar trend was found in Danish data for the same time period[36]. The Nazi occupation of Norway caused many lifestyle changes, including decreased use of polluting vehicles, decreased industrial activity , an increase in physical activity, and an increase in the consumption of vegetables and dietary fiber[29]. These observations suggest that exposure *in utero* and in early childhood to environmental risk factors, including diet and environmental pollution, may be important in the development of testicular cancer.

The association between testicular cancer and male reproductive health is further supported by several investigations suggesting that male reproductive health has been declining since World War II[37]. During the same time period, the incidence of testicular cancer has increased dramatically. A meta-analysis of 61 studies has suggested a substantial decrease in sperm count and semen volume (linked to testicular health) from 1938 to 1990[38]. There are several plausible hypotheses to explain this decline, including environmental chemicals disrupting endocrine function[39], *in utero* exposure to DES and other exogenous hormones[37], and personal factors such as diet change[40] and an increase in sedentary lifestyles[41].

Table 1. Testicular Cancer incidence in selected countries*

Country	Incidence
Switzerland, Graubunden	10.3
Denmark	9.2
Switzerland, Zurich	8.9
Norway	8.0
Germany, Saarland	6.1
USA, SEER: White	5.4
Czech Republic	5.2
Sweden	4.8
UK, England and Wales	4.6
Australia, NSW	4.7
The Netherlands	4.0
Canada	3.8
Peru, Lima	2.9
Finland	2.5
Columbia, Cali	1.7
Hong Kong	1.3
India, Bombay	0.9
USA, SEER: Black	0.7
China, Shanghai	0.7
Uganda, Kyadondo	0.7
Algeria, Setif	0.2

* Data taken from Cancer Incidence in Five Continents Volume VII[26]

2. Etiology

Testicular cancer appears to be preceded by a condition referred to as testicular dysgenesis[42]. Testicular dysgenesis occurs *in utero* and exhibits varying levels of severity, testicular cancer is the most severe. Two conditions have been strongly associated with testicular cancer: cryptochidism/maldescendent testicles[2-17] and carcinoma *in situ*[25;43]. These conditions are thought to be less severe forms of testicular dysgenesis syndrome[42]. Cryptochidism appears to be associated with a degree of maldevelopment of the seminiferous tubules[42]. Carcinoma *in situ* (CIS) is a distinct histological pattern, initiated by the *in utero* environment, which precedes the development of testicular cancer[44]. Fifty percent of patients diagnosed with CIS of the testis develop invasive testicular cancer within five years post-diagnosis[12]. It is thought that all patients who harbour CIS cells at puberty will eventually develop testicular cancer[25].

a) Animal Studies

An important limitation in the understanding of testicular cancer etiology and the role of endocrine modulating substances is in part a result of the controversy surrounding the validity of animal models of human testicular cancer, particularly the mouse[45]. Adult testicular tumors arise from CIS, consist of seminomas and non-seminomas and have consistent chromosomal abnormalities, whereas mouse tumors do not show these traits[45]. It has yet to be determined whether the same genes and molecular level pathways are involved in the development of testicular tumours in mice as in humans. This has been shown for other cancers, notably colon cancer[45-47]. Until this is established in mice, the generalizability of animal research will be unclear and the effect of endocrine toxicants will remain difficult to ascertain.

b) Genetics

The genetic nature of testicular germ cell tumors in adults is well described in the literature[48]. There is strong evidence to support genetic susceptibility to testicular cancer, with an increased risk of testicular cancer among brothers[49 23;50;51], fathers[50;51], and twin brothers[52]. Testicular tumours have a chromosome number in the triploid range, and are characterized by specific chromosomal gains at chromosomes 7, 8, 12, 21, and X, and by specific chromosomal losses at chromosomes 11, 13, and 18[48]. A non-random genetic alteration was localized to i(12p)[53]; a recent study has shown that 80% of testicular tumors have one or more copies of i(12p)[54]. It would seem that isochromosome 12p is the recurrent structural chromosomal abnormality of these tumors[55]. Recently, a susceptibility gene has been localized to Xq27[56]. One study has estimated that 33.4% of all cases of testicular cancer are in individuals with the malignant genotype[51], assuming it is a recessive trait. However, the responsible genotype is not clear. There may be several other potential genetic factors involved in the development or predisposition to testicular cancer[54], which remain undiscovered. The relation of genetic predisposition to endocrine toxicants currently remains unexplored in the peer review literature.

c) In utero exposures

The importance of dysgenesis and CIS in testicular cancer development suggests that the *in utero* environment is very important in influencing risk of carcinogenesis. Several maternal factors, usually involving *in utero* exposures surrogates, have been associated with testicular cancer. An excess of an endogenous hormone, likely estrogen, causes nausea during pregnancy[16]. Nausea in pregnancy has been associated with an increased risk of testicular cancer[18], although some studies have found no such effect[14;16;57 58]. In addition, exposure to estrogen *in utero*[3;16;18] of the fetus has been associated with increased risk of testicular cancer.

Several studies have indicated that children of mothers with high parity have a decreased risk of testicular cancer when compared to children of nulliparous mothers[59-62]. It has been previously suggested that maternal endogenous estrogen levels are higher in first pregnancies as compared to subsequent ones. Since elevated levels of estrogens *in utero* have been found to increase the risk of testicular cancer, it would be expected that first-born sons would be at increased risk as a result of their increased exposure to *in utero* estrogens. Furthermore, it is thought that dizygotic twin pregnancies have higher maternal hormones levels than monozygotic pregnancies[63;64]. Two studies found that dizygotic twins were at an increased risk of testicular cancer[52;65].

Since cigarette smoke has an anti-estrogenetic effect, maternal smoking during pregnancy may decrease the levels of estrogens *in utero*. A study found that sons of mothers who smoked more than 12 cigarettes per day during pregnancy had a lower risk of developing testicular cancer[3]. This protective finding, while not intuitive, could possibly be due to the anti-estrogenic effect of cigarette smoking[66].

The use of exogenous hormones during pregnancy may also increase testicular cancer risk. Specifically, it has been suggested that diethylstilbestrol (DES) use during pregnancy may lead to an increased risk of testicular cancer in male offspring. DES was prescribed to about 4 million pregnant women world-wide from the late 1940s to the early 1970s to prevent abortions and pregnancy complications[37]. Subsequently, DES has been banned as a result of a high incidence of clear-cell adenocarcinoma of the vagina in pubertal girls exposed to DES *in utero*[67]. Currently there is insufficient evidence to support an increased risk of testicular cancer in men exposed to DES *in utero*[37;68;69 70], with only one study reporting an increase in risk[70]. Several

other studies have examined generalized hormone use during pregnancy[3;16;18], although, the hormones considered were not specified.

Few studies have examined the effect of parental occupation on testicular cancer risk in offspring. It is plausible that the occupation of the mother might affect germ cells or the fetus if she were working while pregnant through exposure to pesticides and other chemicals. To date, no studies have found a statistically significant association between testicular cancer and maternal occupation[71;72]. An increase in risk has been found with paternal occupation such as wood processors, metalworkers, stationary engineers, food product workers, metal product workers, and food and beverage service workers[71]. The occupational environments may expose the parent to endocrine toxicants that are transmitted to the child/fetus and increase the risk of testicular cancer.

d) Hormonal Conditions

There are several hormonal conditions within the male that have been associated with an increased risk of testicular cancer: late onset of puberty (a protective effect)[5;8;14;19-21], infertility[21;73-75], and low androgen level[57]. It is unclear whether the association of these conditions implies a common etiologic mechanism or represents part of the causal chain leading to testicular cancer. These risk factors indicate that hormonal balance in the male is important to reduce the risk of testicular cancer, and endocrine toxicants may act to disrupt this delicate balance, and hence increase risk.

e) Diet

Diet and testicular cancer have been associated in several studies[21;76-82]. Despite the inconclusive nature of these findings, a recent article states that "The timing of the testicular cancer trend is consistent with a dietary origin, and the search for candidates should extend

beyond hormonal agents to include those capable of causing genetic damage"[40]. High intake of fat has been associated with increased risk of testicular cancer[77;79;83], which is consistent with many reports for cancers at other hormonally influenced sites such as breast, prostate, colon, and ovary[79;84-86]. This commonality may suggest that the mechanism of carcinogenesis in testicular cancer is similar to those identified for other hormonally influenced sites. Fat intake has been associated with changing hormonal levels and breast cancer risk[87]. Therefore, it may be plausible to assume that fat intake in males has an impact on hormonal levels, influencing testicular cancer risk.

Other foods that have been associated with an increased risk of testicular cancer are dairy products (particularly milk and cheese) [76;78;80;82;88]and meat[76;79;82;83;89]. Milk and dairy products contain of the female sex hormones estrogens and progesterone[90]. It is reasonable to hypothesize that estrogens or progesterone in milk and dairy products may be associated with the development of testicular cancer[78]. This is also supportive of the hypothesis that endocrine modulating substances affect testicular cancer risk. The strength of this association is further supported by the recent trend of increasing testicular cancer incidence and the excessive consumption of dairy productions in developed countries starting in the 1940s and 50s[91]. Another factor contributing to the level of estrogens in dairy products may be the treatment of cattle with hormones and antibiotics, although the impact of this practice on carcinogenesis is unknown. A recent study examined the relationship between dietary intake of phytoestrogens and testicular cancer, but did not observe an association[92].

f) Other exposures

i) Smoking

Smoking has not been extensively examined as a risk factor for testicular cancer. A recent study found a significant and positive association between smoking and testicular cancer risk[93], whereas another other study examining testicular cancer and smoking found no associaton[5].

ii) Vasectomy

Studies from the late 1980s have indicated that there might be an increased risk of testicular cancer after vasectomy (SIR=4.2; CI 1.8-8.2)[94;95]. However, large scale studies have found no association between vasectomy and testicular cancer[7;96;97]. A review of eight articles[98] found only one study suggesting a positive association between vasectomy and testicular cancer.

iii) Occupational exposures

There is a sizable body of literature dealing with the relationship between some types of occupations and testicular cancer risk. Many studies have found positive associations between occupation and testicular cancer[30;99-108]. At risk occupations include: pesticide applicators[99], plastic workers[15;100], farmers[100], metal workers[102;103], professional[30;103;104;106;108], leather workers[105], and work involving asphalt[100]. There is some contention around some of these associations, particularly in farmers. Numerous studies suggest that farming is not related to increased risk[109-113]. Specific occupational exposures have been linked to increased risk of testicular cancer. These include: fertilizers high in nitrogen[114], non-specified chemical fertilizers[75], fumes or smoke[75], pesticides[99;100]. As well, potential exposure to Agent Orange during military service in Vietnam has been associated with an increased testicular cancer risk and diminished semen quality[115].

iv) Physical Activity

The effect of physical activity on testicular cancer risk is unclear. Some studies have found that higher levels of physical activity have a protective effect[8;116], adverse effect[93] or no effect[117].

However, those studies finding a protective effect for physical activity failed to control for diet, while the study finding an adverse effect controlled for some dietary factors[93].

3. Biological Plausibility

The nature of the relationship between exposure to endocrine modulating substances and testicular cancer is unclear. There are several risk factors indicating that exposure to exogenous hormones, through *in utero*, occupational or dietary exposures, may increase the risk of testicular cancer later in life. Although direct human evidence is lacking, the role of endocrine toxicants in testicular cancer development is theoretically possible. This role would be mediated by the estrogenetic or anti-androgenetic effects of hormones on the testicles. However, the types of hormonally active environmental chemicals, the pathways through which they may act, and their implications for cancer remains unknown. Recently, the original suggestion of a link between estrogens and testicular cancer was revisited with five potential mechanisms regarding the role of estrogen and estrogen related compounds and testicular cancer advanced[118].

1. Suppression of androgen production.
2. Suppression of androgen receptor (AR) expression.
3. Suppression of gonadotrophin secretion via enhanced negative feedback by "estrogens".
4. Impairment of Leydig cell development leading to inadequate testosterone production.
5. Suppression of secretion of insulin-like factor-3 (InsL3) by fetal Leydig cells.

4. Conclusion

The etiology of testicular cancer remains largely unknown. The trend of declining male reproductive health and increasing occurrence of endocrine toxicants in the natural environment,

coupled with the hormonal basis of several of the established risk factors for testicular cancer, point towards a hormonal mechanism of carcinogenesis. Currently, there is a lack of direct evidence linking endocrine toxicants and testicular cancer risk. As well, the link between estrogenic or anti-androgenic compounds and testicular cancer has not yet been examined in a rigorous analytic epidemiologic study. In addition, the current lack of a suitable animal model prevents definitive conclusions on the role of hormonally active environmental chemicals on testicular cancer risk.

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