2020

The Association Between Testicular Cancer and Female Reproductive Cancers: A Systematic Review

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THE ASSOCIATION BETWEEN TESTICULAR CANCER AND FEMALE REPRODUCTIVE CANCERS: A SYSTEMATIC REVIEW

by

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A thesis submitted in partial fulfillment of the requirements
for the degree of Bachelor of Science
in the Department of Health Sciences
in the College of Health Professions and Sciences
at the University of Central Florida
Orlando, Florida

Fall Term
2020

Thesis Chair: Michael J. Rovito

ABSTRACT

The most common neoplasm found in young to middle-aged men is testicular cancer (TCa). This disease not only poses a risk of early death, but can also affect a male's fertility and testosterone levels and can diminish one's mental health and/or quality of life. One particular line of research that is emerging in the field is a possible genetic association of TCa with female reproductive cancers. We employed a systematic review to assess the methodological quality of articles that met the inclusionary criteria. To be selected for this review, articles had to go through a primary, secondary, and tertiary screening procedure using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines. Four studies were selected, and the Newcastle-Ottawa Scale (NOS) was used to measure the quality of each nonrandomized, case-control or cohort study. Two articles received perfect scores, one case-control study received a near-perfect score of 8 out of 9 stars, and only one out of the four included studies received 5 out of 9 stars. Upon organizing and analyzing the data, we found a significantly increased risk (20%) of female reproductive cancer among women who had a father with TCa. Also, we found that men were 12% more likely to develop TCa if they had a sister with female reproductive cancer, and 16% more likely if their mother had ovarian, endometrial, breast or cervical cancer. The goal of this review was to assess the overall strength of association, or lack thereof, between TCa and female reproductive cancers. Findings of this review suggest that an association exists between these discordant forms of cancer. There were significant risks found between mothers and sons, backed by substantial evidence of an X-linked inheritance pattern. This information has the potential to improve our knowledge of cancer etiology and treatment.

Keywords: testicular cancer, neoplasms, epidemiology, mortality, female reproductive, ovarian, gonadal, familial association, genetic predisposition, inheritance

ACKNOWLEDGMENTS

I would like to sincerely thank Dr. Michael Rovito and Dr. Eunkyung Lee for their dedication to this project. They are both incredibly caring, hardworking, and talented mentors. I would not have been able to complete this thesis without their devotion to higher education and their students.

I would also like to thank my family for inspiring and motivating me every day to work towards my goals.

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Testicular cancer (TCa) is defined as a malignancy that develops in the tissue of one or both testes (National Cancer Institute, 2019). TCa is a relatively rarer cancer throughout the world but is the most common neoplasm in men aged 14 to 44 (Cheng et al., 2018). The most common type of testicular malignancy is known as testicular germ cell tumors (TGCT), caused by a neoplasm derived from germ cells (McGlynn et al., 2010).

Over the last 40 years, the incidence of TCa has been increasing at a steady rate, primarily among Caucasian males (Park et al., 2018). Currently, TCa accounts for roughly 1-1.5% of all cancers in the global male population, and is the most common malignancy in young adult men aged 20-40 years old (Boccellino et al., 2017).

Potential Causal Factors

Family history is the greatest risk factor for developing TCa, possibly due to shared environmental exposure, or an X-linked/autosomal recessive genetic trait (Pyle et al., 2016). A few other causal factors of TCa are cryptorchidism, premature birth, low birth weight, and twinning (Smith et al., 2018). It is also possible that women with high estrogen levels during gestation may be at risk of having sons with TCa (Piltoft et al., 2017).

Female Reproductive Cancer Associations

Research suggests that TCa may be the result of X-linked inheritance, with a genetic susceptibility trait located near an ovarian cancer susceptibility trait on the X-chromosome (Etter et al., 2018). In a recent study, the researchers at the Roswell Park Cancer Institute (2018) discovered an association between TCa and familial ovarian cancer by analyzing data from an ovarian cancer registry. By examining the medical histories of 34 males with a prior TCa diagnosis, these men were more likely to have a mother or sister with familial ovarian cancer, compared to males with other cancer types (Etter et al., 2018). Another study suggests that, although rare, there are familial associations between female breast cancer and TCa (Zheng et al., 2017).

Objectives

To the authors' knowledge, however, no systematic review of literature exists that examines the association between TCa and female reproductive cancers. The goal of this systematic review, therefore, was to determine the methodological quality of studies aiming to demonstrate the possible associations between TCa and female reproductive cancers. Future directions and recommendations will be offered to guide future studies in this specific line of research.

Research Question

Does an association exist between TCa and the various forms of female reproductive cancers?

Review of Literature

Testicular Cancer Overview

Testicular cancer (TCa) is a rare malignancy but most prevalent among men of European descent, typically aged 15 to 44 (Znaor et al., 2020). Specifically, Scandinavian men have rates of testicular cancer 5 to 10 times greater than those of Asian and African ancestry (McGlynn et al., 2010).

According to one article, “There has been an increase in the incidence of testicular cancer in many Western countries over the past 40 years and the global incidence of testicular cancer has doubled over the past three decades” (Manecksha & Fitzpatrick, 2009). Epidemiology of testicular cancer. BJU international, 104(9b), 1329-1333. Specifically, between 1973 and 2002, white American men experienced a 52% increase in the incidence of TCa (Chia et al., 2010). Additionally, research shows that Eastern Europe is predicted to see a 32% increase in TCa cases between 2010 and 2035 (Znaor et al., 2020).

Epidemiology and Prevalence

In 2020, there were an estimated 9,610 new cases of TCa, with 440 estimated deaths in the United States alone (American Cancer Society, 2020). In addition, the incidence among U.S. men rose by roughly 19% from 1992 (5.7 per 100,000) to 2009 (6.8 per 100,000) (Nigam et al., 2015). Luckily, medical advancements have improved the 5-year survival rate of TCa to 97% from 2005 to 2011 (Siegel et al., 2016).

However, the incidence of TGCT in Maori men of New Zealand is much more prevalent. In 2002, Maori men had 10.6 cases per 100,000, in contrast to non-Maori men who had significantly less cases, with 3.5 per 100,000 (New Zealand Health Information Service 2006).

Etiology and Risk Associations

Testicular germ cell tumors (TGCT) are believed to develop from intratubular germ cell neoplasia (IGCN), commonly known as carcinoma in situ (CIS) (Batool et al., 2019). Roughly 98% of all TGCTs develop from germ cells, with more than half being seminomas (55%), while the remaining are nonseminomas (44%) and spermatocytic seminomas (1%) (McGlynn et al., 2010).

Pre-existing medical conditions seem to pose a risk of TGCT development in addition to race/ethnicity (McGlynn et al., 2010). Cryptorchidism, commonly known as undescended testicle(s), is the disorder most closely related to the formation of testicular cancer (Smith et al., 2018). Patients diagnosed with cryptorchidism are about 4.3 times more likely to develop TGCT than patients without (Cook et al., 2010). While there is no definitive relationship, research shows that there may be genetic components that increase the likelihood of developing TCa among brothers and sons of affected individuals (Batool et al., 2019).

Female Reproductive Links

Family history of TCa is a risk factor for developing TCa (Smith et al., 2018). However, it is unknown if female reproductive cancers are a risk factor for testicular

cancer in males. Etter and colleagues (2018) state that there is “evidence for several susceptibility genes, including 27 identified autosomal loci and a putative X-linked gene at Xq27, *TGCT1*” (p. 184). This indicates a possible familial association between male and female genitourinary tract anomalies.

In the past three decades, research has been conducted with results linking TCa to the X-chromosome (Looijenga et al., 1997). This is significant because human males normally have one X chromosome and one Y chromosome, obtaining one sex chromosome from each parent. Therefore, male offspring will receive their X chromosome from the mother, and their Y chromosome from the father.

Interestingly enough, Eng and colleagues (2018) identified that this X-linked testicular cancer susceptibility gene is located in close proximity to an ovarian cancer susceptibility gene (Eng et al., 2018). This further proves that these recognized familial germ cell neoplasms are driven by this X-linked gene.

Giambartolomei and colleagues, “found evidence of familial [ovarian germ cell tumor] clustering, both site-specific and in combination with TGCT, and noted distinct histologic patterns for ovarian germ cell tumors (OGCT) and TGCT, by age.” (Giambartolomei et al., 2009, pg. 5). They claim this supports the theory that ovarian germ cell tumors may be a rare manifestation of familial gonadal tumor syndrome. Another study by Zheng and colleagues (2017) suggests, albeit rare, familial associations may be present between female breast cancer and TCa.

This accumulating evidence implies that associations between TCa and female reproductive cancers may exist. Further investigation is needed to discover definitive manifestations of familial gonadal tumor syndrome.

Methods

Study Design

A systematic review was employed to assess the methodological quality of qualified articles to assess the strength of association between the manifestation of TCa and a family history of female reproductive cancers. Each article was analyzed using the Newcastle-Ottawa Scale (NOS) to measure the quality of each study. Sources were screened and selected by following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines (Liberati et al. 2009).

Data Reference and Search Strategy

The Medical Subject Headings (MeSH) database was used to index articles and develop keywords to search pertinent literature. The Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1990 to present), PubMed (1990 to present), ProQuest (1990 to present), and Google Scholar (1990 to present) databases were used to find literature relevant to this study. Keywords used to search literature included variants of testicular cancer, neoplasms, epidemiology, mortality, female reproductive, ovarian, gonadal, familial association, genetic predisposition, and inheritance.

Study Selection

Inclusion and Exclusion Criteria

Studies were required to meet the following inclusionary criteria to be evaluated in the systematic review and assessed using the NOS. Only peer-reviewed, scholarly

articles were included in the screening process. Articles had to be epidemiologically-focused analytical studies showing associations between testicular cancer and female reproductive cancers in order to be accepted.

Genetically-focused articles that focus solely on the pathophysiological processes of TCa were excluded from the systematic review. Furthermore, drug patents, medical procedures, case studies, review papers, and interventions were also rejected. Non-peer reviewed articles were excluded from the screening procedure.

Screening Procedure

The PRISMA flow diagram was used to organize the flow of selection of studies while screening peer-reviewed journals. This tool was used to map out the number of studies included or excluded in each primary, secondary, and tertiary screening stage. The qualifying studies were assessed using the following screening guidelines:

Primary Screening

First, titles and abstracts were screened based upon their relevance to the study objectives. Any articles showing an association between testicular cancer and other cancers were kept for further screening. Non-peer reviewed articles and unpublished materials were excluded.

Secondary Screening

Then, full articles were screened for relevance. Articles showing a link between testicular cancer and the main types of female reproductive cancer were kept for further

screening. Female reproductive cancers are inclusive of cervical, ovarian, uterine, endometrium, vaginal, vulvar, and breast cancer (Mun et al., 2015).

Tertiary Screening

Last, articles that showed definitive evidence of an association between TCa and female reproductive cancer were kept for the data extraction. These articles were then assessed using the NOS.

Data Extraction and Methodological Quality Assessment

Overview

The articles deemed relevant were scored using the NOS, to measure the quality of nonrandomized studies, including, but not limited to, case-control and cohort studies.

Data Extraction and Quality

The information collected from each study included study design, number of human subjects, confounding variables and method of control. Additional information consisted of TCa characteristics identified, which female reproductive cancers were investigated, and results and data. The results were summarized by utilizing an odds-ratio and confidence interval. The NOS assessed the methodological quality of cohort and case-control studies with nine evaluation items on the adequacy of the recruitment/selection process of study participants (4 items), comparability of comparison groups (2 items), and exposure/outcome ascertainment (3 items).

Results

Publications Identified

Search Strategy

Multiple searches were conducted using the Cumulative Index to Nursing and Allied Health Literature (CINAHL; 1990 to present), PubMed (1990 to present), ProQuest (1990 to present), and Google Scholar (1990 to present) databases using the keywords testicular cancer, neoplasms, epidemiology, mortality, female reproductive, ovarian, gonadal, familial association, genetic predisposition, and inheritance.

Search Results

These searches returned approximately 3,780 results (Figure 1). Once the duplicates were removed, there were 3,402 records remaining. Any patents, clinical trials, or other studies that did not have a cohort or case-control study design were rejected (n = 2,374). Next, titles and abstracts were screened based upon their relevance to the thesis, while non-peer reviewed articles and unpublished materials were excluded (n = 786). Any articles showing an association between TCa and other cancers were kept for secondary screening. Of the remaining 242 records, full articles were screened for relevance. Articles that displayed an association between TCa and the main types of female reproductive cancer (cervical, ovarian, uterine, vaginal, vulvar, and breast cancer) were kept for tertiary screening (n = 12). Last, articles that showed definitive evidence of an association between TCa and female reproductive cancer were

kept for the systematic review (n = 4). These articles were then assessed using the NOS quality assessment tool.

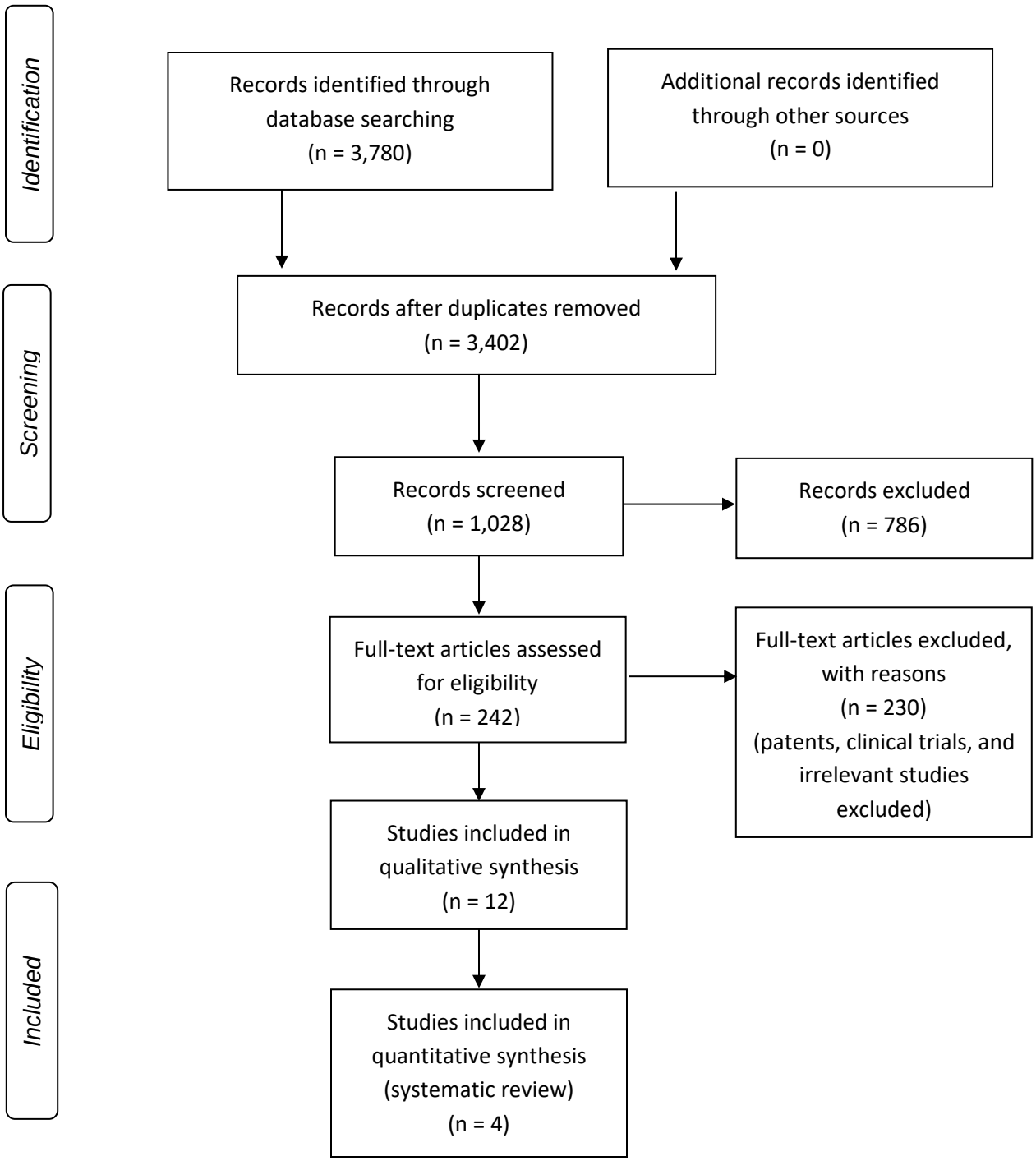


Figure 1. PRISMA Flow Diagram.

Included Studies

There were four studies that met the eligibility requirements for the systematic review (Table 1). This was inclusive of two cohort studies (Zheng et al., 2017; Hemminki et al., 2005), and two case-control studies (Etter et al., 2018; Nordsborg et al., 2011). Each study was evaluated using the NOS scale. Three out of the four studies (Zheng et al., 2017; Hemminki et al., 2005; Nordsborg et al., 2011) achieved a good quality score. There was only study (Etter et al., 2018) that received an acceptable quality score of 5 out of 9 stars.

The measures of association were depicted in an estimated hereditary risk table (Table 2). This table illustrates the estimated risk of a first-degree relative with either TCa or female reproductive cancer. The data is organized as two groups of hereditary directionalities (male to female; female to male), separated into five subgroups (father to daughter; brother to sister; son to mother; sister to brother; mother to son). For example, the risk ratio of female breast cancer was 1.14 (95% CI 1.00-1.30) for women who had a father with TCa. The estimated risk of each hereditary directionality was then calculated by meta-analysis using random effects models averaging the ratios associated with their corresponding subgroup.

The average estimated risk (shown in Table 2) of female reproductive cancer was found to be 20% higher in women who had a father with TCa. Women who had a brother with TCa were only 1% more likely to develop female reproductive cancer. There was no significant association found between women with female reproductive cancer who had sons with TCa. Men who had a sister with female reproductive cancer

were 12% more likely to develop TCa, and 16% more likely if they had a mother with ovary, endometrium, breast or cervix cancer.

Table 1. Study summaries of 4 articles included in systematic review.

Author Name(s)	Etter	Nordsborg	Zheng	Hemminki
Date	2018	2011	2017	2005
Study Design	Familial case-control	Population-based case-control study	Cohort	Cohort
Region of Study	USA	Denmark	Sweden	Sweden
Number of Participants	2,636 families with multiple cases of ovarian cancer	9,891	76,060 female offspring with BC (12266 families)	175,635 off springs
Data source	Familial Ovarian Cancer Registry	Danish Cancer Registry for cases and Danish Civil Registration System for controls	Swedish Family-Cancer Database	Swedish Family-Cancer Database
Age (years)		Median 35 (0-96)	0-70	0-70
Cases	34 men with testicular cancer	3,297 with testicular cancer		
Controls	2,894 men with non-testicular cancer	6,594 matched controls		
Exposure	First-degree relatives (FDR) with ovarian cancer	First-degree relatives with other cancers		
Outcome			Familial cancer risk in offspring/FDR in two ways	Familial cancer risk in offspring/FDR in two ways
Follow-up Period				1958-2002
Incidence				4,586 TC in sons and 4315 in fathers
Confounder Included in Study	None - univariate logistic regression	Number of relatives	Age group, sex, calendar period, residential area, and SES	Age, sex, tumor type, period, ses, residential area
Quality Score	**5**	**8**	**9**	**9**

Table 2. Measures of association of the estimated hereditary risk.

	Male to female			**Female to male**	
Hereditary Directionality	*Father's with TCa → daughter's with female reproductive cancer*	*Brother's with TCa → sister's with female reproductive cancer*	*Sons with TCa → mother's with female reproductive cancer*	*Sister's with female reproductive cancer → brother with TCa*	*Mother's with female reproductive cancer → son's with TCa*
Risk Ratio	RR for breast cancer = 1.06 (0.86-1.31) when any FDR* had TCa	RR for breast cancer = 1.14 (1.00-1.30) when brother had TCa	RR for breast cancer = 1.06 (0.86-1.31) when any FDR* had TCa	RR for TCa = 1.66 (0.87-3.15) when sister had ovary cancer	RR for TCa = 3.32 (1.46-7.55) when mother had ovary cancer
	RR for female genital organ cancer = 0.89 (0.68-1.16) when any FDR* had TCa	RR for breast cancer = 0.90 (0.66-1.22) when brother had TCa	RR for female genital organ cancer = 0.89 (0.68-1.16) when any FDR* had TCa	RR for TCa = 1.14 (1.06-1.23) when sister had breast cancer	RR for TCa = 1.14 (1.06-1.23) when mother had breast cancer
	RR for breast cancer = 1.14 (1.00-1.30) when father had TCa	RR for cervix cancer = 1.68 (0.87-3.24) when brother had TCa		RR for TCa = 0.98 (0.63-1.52) when sister had breast cancer	RR for TCa = 1.17 (0.98-1.39) when mother had breast cancer
	RR for breast cancer = 1.28 (0.85-1.92) when father had TCa	RR for endometrium cancer = 1.09 (0.50-2.38) when brother had TCa		RR for TCa = 0.80 (0.31-2.07) when sister had cervix cancer	RR for TCa = 0.74 (0.44-1.25) when mother had cervix cancer
	RR for cervix cancer = 0.69 (0.19-2.54) when father had TCa	RR for ovary cancer = 0.97 (0.44-2.14) when brother had TCa		RR for TCa = 1.34 (0.45-3.98) when sister had endometrium cancer	RR for TCa = 1.05 (0.70-1.57) when mother had endometrium cancer
	RR for endometrium cancer = 1.52 (0.51-4.49) when father had TCa			RR for TCa = 1.11 (0.43-2.88) when sister had ovary cancer	RR for TCa = 1.14 (0.76-1.71) when mother had ovary cancer
	RR for ovary cancer = 0.75 (0.20-2.75) when father had TCa				
Average Estimated Risk	**1.20**	**1.01**	**--**	**1.12**	**1.16**

*FDR = first-degree relative

Discussion

Summary

The Newcastle-Ottawa assessment scale is well-known for determining the quality scores of articles and assessing the risk of bias. A ‘star-system’ is utilized to measure the quality of cohort and case-control studies. This systematic review preferred the NOS tool, in order to measure the quality of articles that showed an association between TCa and female reproductive cancers. Each article that passed the tertiary screening process was analyzed using the NOS to measure the quality of nonrandomized study. This quality assessment tool utilizes a ‘star system’ to evaluate the study group selection, comparability, and ascertainment of the exposure or outcome of interest.

Systematic Review Findings

A total of four studies were eligible for use in the systematic review (Zheng et al., 2017; Hemminki et al., 2005, Etter et al., 2018; Nordsborg et al., 2011). Church and colleagues deliberated in order to agree upon a score for each selected study. Two articles (Zheng et al., 2017; Hemminki et al., 2005) received perfect scores (shown in Table 3) according to the NOS requirements. In other words, these two studies contained quality selection of groups, comparability, and ascertainment of outcomes. This signifies that both of these studies were of good quality. One case-control study (Nordsborg et al., 2011) received a near-perfect score of 8 out of 9 stars, due to the lack

of non-response rate provided (Table 4). However, this is still considered to be a study of good quality. Only one out of the four included studies (Etter et al., 2018) was found to be of acceptable quality. This conclusion was met due to a lack of comparability, ascertainment of exposure, and non-response rate (Table 4).

Table 3. Methodological quality assessment of cohort studies included in the systematic review.

	Methodological Quality Assessment									
	Selection				Comparability		Outcomes			
Author, year	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**Total score†**
Zheng, 2017	*	*	*	*	*	*	*	*	*	9
Hemminki, 2005	*	*	*	*	*	*	*	*	*	9

Selection (4*):
A = Representativeness of the exposed cohort in the community
B = Selection of the non-exposed cohort from the same community as the exposed cohort
C = Ascertainment of exposure through secure record or structured interview
D = Demonstration that outcome of interest is not present at the start of the study
Comparability (2*):
E = Comparability of cohorts on the basis of the design or analysis
F = Comparability of cohorts on the basis of the design or analysis
Outcome (3*):
G = Assessment of outcome through blind assessment or record linkage
H = Was follow-up long enough for outcomes to occur
I = Adequacy of follow-up of cohorts to ensure losses are independent of the exposure or the outcome

Table 4. Methodological quality assessment of case-control studies included in the systematic review.

	Methodological Quality Assessment									
	Selection				Comparability		Exposure			
Author, year	**A**	**B**	**C**	**D**	**E**	**F**	**G**	**H**	**I**	**Total score†**
Etter, 2018	*	*	*	*	-	-	-	*	-	5
Nordsborg, 2011	*	*	*	*	*	*	*	*	-	8

Selection (4*):
A = Is the case definition adequate through independent validation
B = Representativeness of the cases
C = Selection of controls from community
D = Definition of controls: No history of disease
Comparability (2*):
E = Comparability of cases and controls on the basis of the design or analysis
F = Comparability of cases and controls on the basis of the design or analysis
Exposure (3*):
G = Ascertainment of exposure through secure record or blinded interview
H = Same methods of Ascertainment for cases and controls
I = Non-response rate: Same rate for both groups

Key Findings

Upon calculating the average estimated risk for each subgroup (shown in Table 2), we can infer that males are 16% more likely to develop TCa when their mother has female reproductive cancer (inclusive of ovarian, breast, cervix and endometrial cancer). This may be due to a probable X-linked trait passed from mother to son. As previously stated, one study identified an X-linked TCa susceptibility gene in close proximity to an ovarian cancer susceptibility gene (Eng et al., 2018). This further proves that an association exists between TCa and female reproductive cancer.

By compiling the available data into forest plots (Figures 2 through 5), the risk of discordant cancer inheritance was concluded. The hereditary risk of developing TCa was found to be 14% higher among men who had a mother or sister with female reproductive cancer (shown in Figure 2 and Figure 4).

Additionally, the limited number of eligible studies may not fully reflect each individual risk. For example, the risk of female reproductive cancer was merely 8% higher in women with a father or brother that had TCa (shown in Figure 3 and Figure 5). However, because evidence is sparse, this may actually indicate a clinically significant risk factor.

There are other variables that must be considered. Mother’s and son’s may be more likely to both develop these forms of cancer due to shared behavioral or environmental factors.

Figure 2. Heredity Estimation of Testicular Cancer When Mother or Sister has Cancer

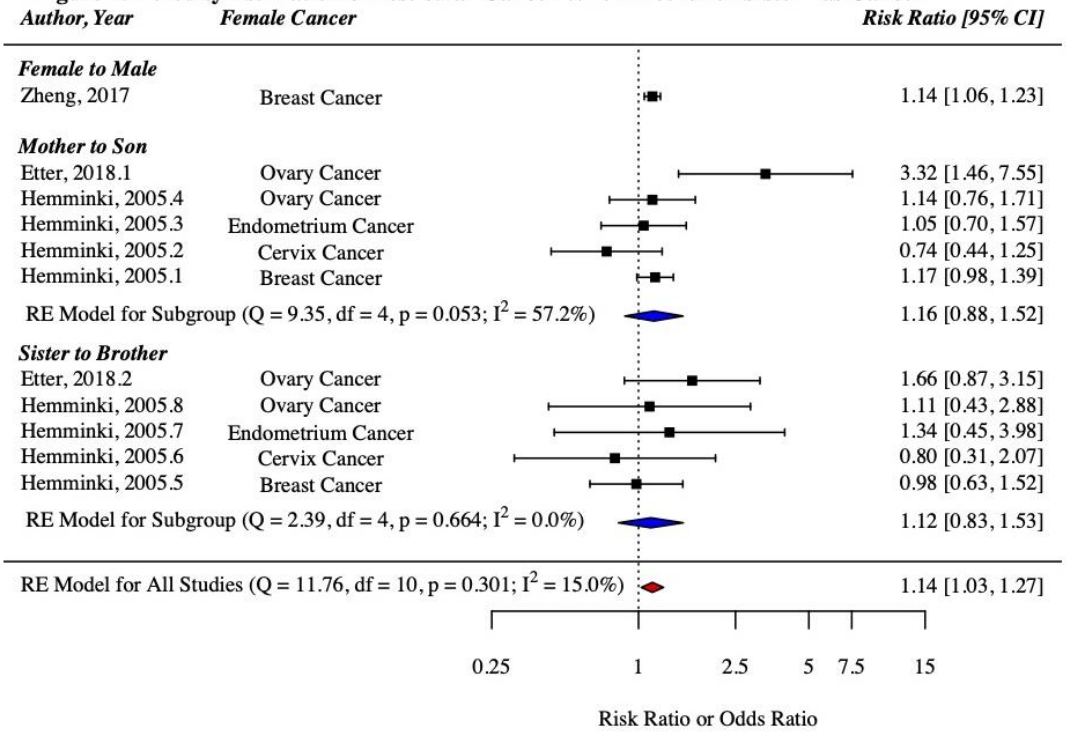


Figure 3. Heredity Estimation of Female Cancer When Father or Brother has Testicular Cancer

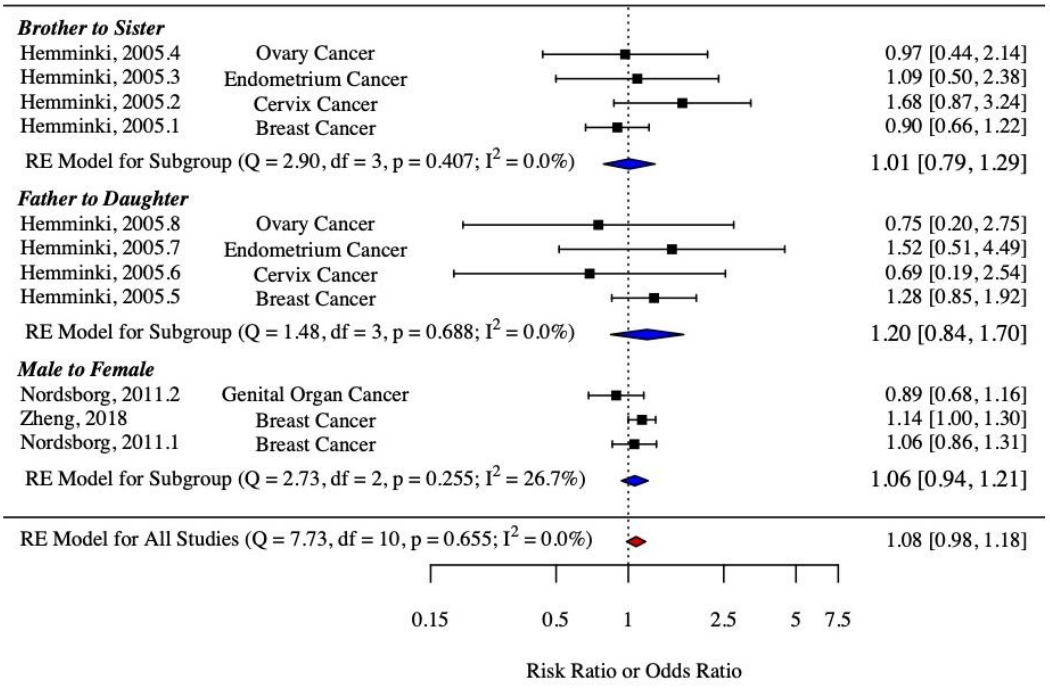


Figure 4. Heredity Estimation of Testicualr Cancer When Mother or Sister Has Cancer

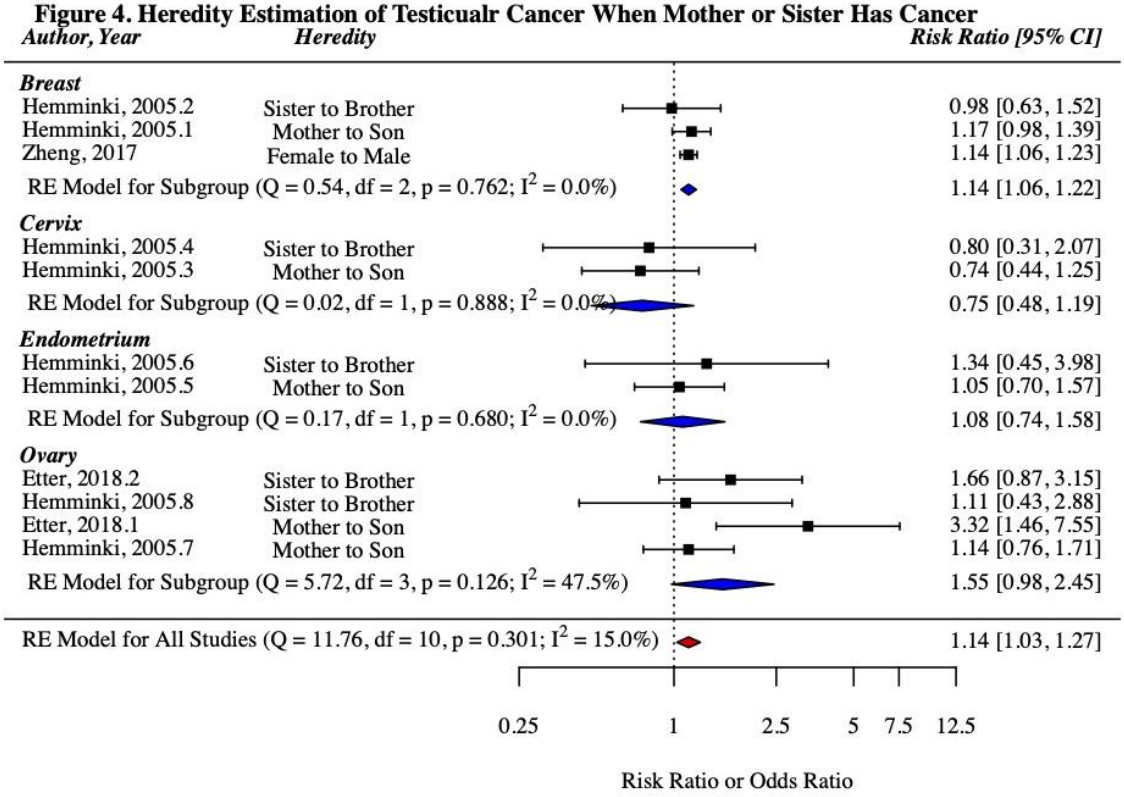
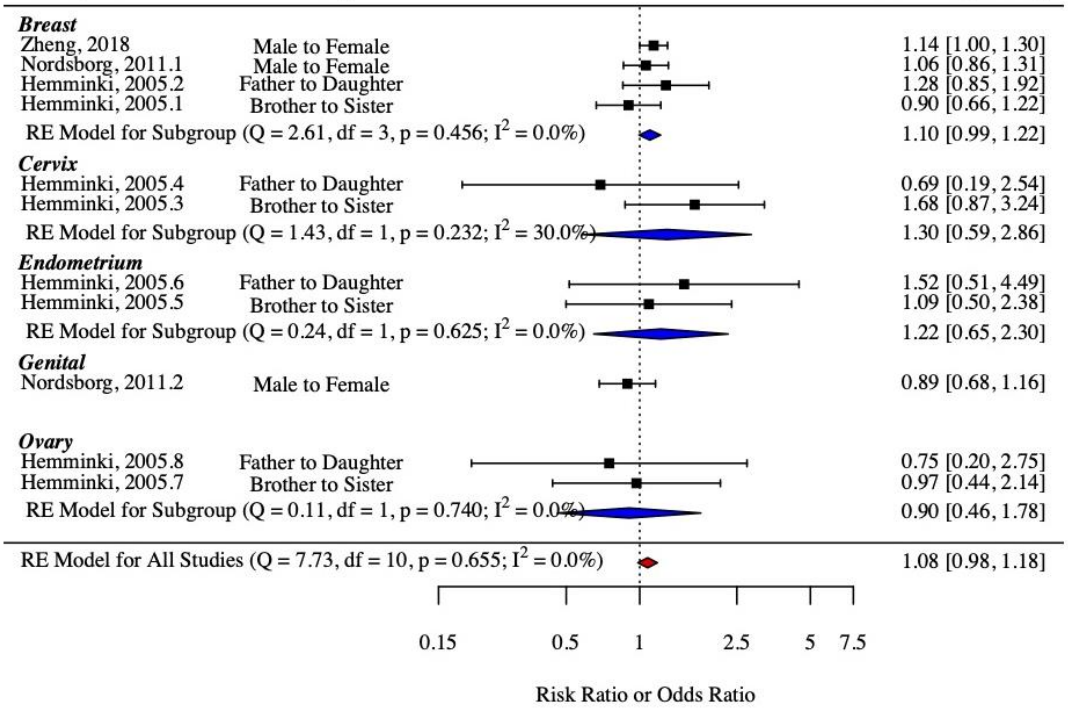


Figure 5. Heredity Estimation of Female Cancer When Father or Brother has Testicular Cancer



Strengths and Limitations

This systematic review was not without its own limitations. It proved challenging to find articles that met the eligibility requirements. To the authors knowledge, there is no other systematic review of literature that examines the association between TCa and female reproductive cancers. This is still a novel and developing field of study, so there is a very limited amount of epidemiological analytical studies focused on the associations between these discordant cancers. More studies must be conducted to achieve more accurate results.

Conclusion

The purpose of this study was to determine the methodological quality of nonrandomized studies showing any possible associations between TCa and female reproductive cancer. Findings of this review suggest that an association exists between these discordant cancers. There were significant risks found between mothers and sons, backed by substantial evidence of an X-linked inheritance pattern. We hope to bring attention to this field of study so that more definitive evidence may be derived. This developing topic has the potential to improve our knowledge of cancer etiology and treatment.

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