Sex Disparities in Adult and Childhood Cancer Incidence

by
Stephanie Fisher

A PROJECT

submitted to

Oregon State University

University Honors College

in partial fulfillment of
the requirements for the
degree of

Honors Baccalaureate of Science in Public Health
(Honors Scholar)

Presented November 18, 2014
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Studies indicate that many cancers occur more frequently in adult males than females. This male predominance must either be due to disparate environmental exposures or innate, biologic mechanisms, or a combination of the two. Using data and statistical software from the Surveillance, Epidemiology, and End Results (SEER) Program, male:female incidence rate ratios were calculated for 86 cancer sites in adults and 60 cancer sites for childhood cancers. About 95% of the adult cancer sites and 55% of the childhood cancer sites showed increased incidence in males. The finding of a male predominance in childhood cancers weakens the argument that unequal environmental exposures are the cause of the overall sex disparity.

Key Words: sex disparities, cancer incidence, childhood cancer, SEER

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I understand that my project will become part of the permanent collection of Oregon State University, University Honors College. My signature below authorizes release of my project to any reader upon request.

Stephanie Fisher, Author

Introduction

Most cancers have male to female incidence rate ratios (IRRs) greater than one, and some of the most common cancers have the highest IRRs; lung and bronchus cancers have an IRR of 1.52 and colorectal cancers have an IRR of 1.35 (Dorak & Karpuzoglu, 2012). Men also have a higher overall likelihood of developing cancer, even though they have shorter life expectancies (44.8% lifetime risk, compared to women's likelihood of 38.1%; Dorak & Karpuzoglu, 2012). This predominance must either be due to disparate environmental exposures or innate, biologic mechanisms, or some combination of the two, such as epigenetics (Edgren, Liang, Adami, & Chang, 2012).

Historically, researchers have pointed to more frequent malignant behavior and occupational exposures of men and more willingness among women to seek medical help as the most likely reasons for the sex difference in incidence (Biggar, Bergen, & Poulsen, 2009; Micheli et al., 2009). A purely environmental stance would have to be supported with environmental risk factors for each cancer site that affect one sex more than the other (Biggar, Bergen, & Poulsen, 2009). Edgren, Liang, and Adami (2012) looked at 35 cancer sites along with their known risk factors, like alcohol and tobacco consumption, and analyzed how fully the cancer could be explained by these factors. Thirteen of those sites could not even be partly explained by known environmental risk factors and were described by the researchers as having an "enigmatic" disparity. This is the basis for the first question of this study: is there a male predominance found in each cancer site using the most recent U.S. cancer incidence data available, especially the thirteen noted to be enigmatic by Edgren and colleagues?

Some researchers are leaning more toward a biologic and physiologic explanation for the male predominance. Sex hormones, gene expression regulation, and immune surveillance mechanisms are some of the innate, biologic factors researchers are beginning to focus on (Dorak & Karpuzoglu, 2012). For example, Dorak and Karpuzoglu (2012) explain the differences between men and women in immune response to infection and in autoimmune diseases, and how this could contribute to the observed male predominance of cancer incidence and mortality. If this epigenetic, biologic stance is to be favored over the environmental stance that has previously dominated the explanation for male predominance, then childhood cancers should also show a male predominance. This is the basis for the second question addressed in this study: does the male predominance hold true in childhood cancers?

In summary, the present study seeks to shed light on the mystery of male predominance in cancer incidence by investigating two topics: male predominance at each cancer site among adults, and male predominance in cancers among children.

Methods

The data and statistical software used for this study came from the Surveillance, Epidemiology, and End Results (SEER) Program created by the National Cancer Institute. The SEER program collects demographic information such as sex, race, and age at cancer diagnosis, in addition to cancer history information, including primary site, stage, and tumor morphology (SEER, 2014). The present study used the most current SEER 9 database from November 2013, which has information collected from 1973 to 2011 covering about 28% of the US, including Connecticut, Detroit, Atlanta, Iowa, New

Mexico, Utah, the Seattle-Puget Sound area, the San Francisco-Oakland area, and Hawaii (see red in figure 1; SEER, 2014). Although the SEER 9 covers less area than the other databases, its data is the most consistent and goes back the farthest.

The statistical software SEER*Stat was used to access the SEER database and to calculate age-adjusted rates. Two SEER*Stat rate sessions were run to generate male and female incidence rates for malignant cancers for the total population and for ages 0-14 years. To address the question about total cancer incidence by gender, a rate session was executed using the ICD-0-3 cancer groupings (recoded by SEER*Stat for ICD-0-3/WHO 2008) to produce male and female rates per 1,000,000 people. This resulted in 101 cancer specific rates, of which 15 were primary or secondary sex organs and were excluded from the analysis. To address the question about childhood cancers, a rate session was executed using the ICCC3 cancer site recode provided by SEER*Stat and age at diagnosis limited to 0-14 years to produce male and female rates per 1,000,000 people. This produced 60 rates, all of which were kept in the analysis. From these two rate sessions, rates were checked against published SEER rates and male to female rate ratios (IRRs) were computed by dividing the male rate for a site by the female rate for the site using an Excel spreadsheet.

Results

A total of 86 major and specific cancer sites were included in the analysis for adult cancers and all 60 cancer sites were included for childhood cancers. The adult cancers had IRRs ranging from 0.15 (Peritoneum, Omentum and Mesentery cancer) to 27.17 (Kaposi Sarcoma) and the childhood cancers had IRRs ranging from 0 (Gonadal

carcinomas and other and unspecified malignant gonadal tumors) to 4.75 (Burkitt lymphoma). For total cancers, the IRR was 1.35. For the 16 adult cancer sites, all but the endocrine system cancer had an IRR over 1 (see Table 1). The 86 adult cancer sites were broken into groups based on the IRR: below 1, 1.01-1.25, 1.26-1.50, and so on. Figure 2 shows the breakdown of IRRs based on these groupings, with 5 IRRs (6%) below 1.00, 56 IRRs (65%) between 1.01 and 2.00, 14 IRRs (16%) between 2.01 and 3.00, 6 IRRs (7%) between 3.01 and 4.00, and 5 IRRs (6%) 4.01 and above. In other words, 81 (94%) of the 86 adult cancer sites had IRRs over 1.00.

For the 13 major childhood cancer groups, 8 (62%) had IRRs over 1 (see Table 2). The 60 childhood cancers IRRs were broken down in the same way as the adult cancers in Figure 3, depicting 19 of the IRRs (32%) below 1.00, 4 IRRs (7%) at 1.00, 30 IRRs (50%) between 1.01 and 2.00, and 2 IRRs (3%) above 2.01. Four of the sites (7%) had incidence rates of 0 for both males and females, and 1 site (2%; Myelodysplastic syndrome and other myeloproliferative cancers) had a female incidence rate of 0 and thus an undefined IRR. In sum, 33 of the 60 specific childhood cancer sites (55%) had IRRs over 1.00 and 19 (32%) had IRRs below 1.00.

Discussion

With 94% of the adult cancer sites and 55% of the childhood cancer sites having IRRs above 1, the present study's results reflect the existing literature on male predominance in the majority of cancer types. Of the thirteen sites deemed to have an "enigmatic" disparity by Edgren and colleagues (2012) (tonsillar, thyroid, nasopharyngeal, stomach, lymphoid leukemia, rectal, myeloid leukemia, non-melanoma

skin, multiple myeloma, small intestinal, non-Hodgkin lymphoma, brain and nervous system, and Hodgkin), only one (thyroid) had an IRR below 1 (see table 3). This means that even the cancers that cannot be explained by known risk factors largely have a male predominance in incidence, offering support for the biologic or epigenetic perspective on this sex disparity.

The male predominance of childhood cancers was less pronounced but still existed. Ward, Desantes, and Robbins (2014) noted in their childhood cancer review that overall, incidence rates are higher in males and that existing research has not been able to consistently identify an environmental cause. The present study's finding of a male predominance in childhood cancers weakens the argument that unequal environmental exposures are the cause of the overall sex disparity because children diagnosed with cancer have not had the time to accumulate the exposures, especially the workplace exposures often pointed to. This supports Dorak and Karpuzoglu's (2012) conclusion that because children have not had as much exposure to environmental carcinogens, a male predominance must at least in part be attributed to genetics.

Thyroid cancer is the one adult site with a male to female (M:F) IRR below 1 as well as one of the few childhood cancer sites with an M:F IRR below 1. It has been extensively studied with only estrogen levels consistently identified as a potential cause of female predominance (Rahbari, Zhang, & Kebebew, 2010). Higher estrogen levels are one of the biologic mechanisms that seem to be protective in many situations, such as in the identification and removal of pathogens and in some cancers like melanoma, but harmful in others situations, such as being a risk factor for autoimmune diseases and thyroid and breast cancer (Dorak & Karpuzoglu, 2012; Micheli, et al., 2009). This

biologic/physiologic explanation for the sex disparity in thyroid cancer is strengthened with the evidence of the childhood thyroid site also with the IRR less than 1. Similarly, nasopharyngeal cancers have high M:F IRRs in both adults (2.49) and children (4.00), and thus an environmental exposure accumulation is unlikely to be the cause of the sex disparity in this cancer site.

The current study is limited in its scope as it only looked at incidence rate ratios and did not evaluate potential causes of the observed disparities. The use of IRRs instead of comparing crude incidence rates is a strength of the study, as IRRs account equally for changes in diagnostic and prevention strategies and other non-sex specific changes (Cook et al., 2009). Future research should investigate each histologic site for the cancer sites with the highest and lowest M:F IRRs to see if the male or female predominance holds true at each site, as answers to the unexplained disparities with the extreme IRRs would offer the most clarity on the environmental versus biologic argument. Additionally, future research in causes and patterns of cancer should analyze by sex to monitor the sex disparities observed in the present study.

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Appendices

Adult Cancer Sites from SEER 9 Database (1973-2011)			
Cancer Site	Male Incidence Rate	Female Incidence Rate	Male to Female IRR
Kaposi Sarcoma	32.6	1.2	27.17
Mesothelioma	18.4	3.9	4.72
Urinary System	547.0	177.3	3.09
Oral Cavity and Pharynx	179.5	69.7	2.58
Respiratory System	960.4	475.9	2.02
Leukemia	174.2	101.7	1.71
Myeloma	71.3	47.1	1.51
Digestive System	1,143.6	764.8	1.50
Skin excluding Basal and Squamous	221.3	149.2	1.48
Lymphoma	252.8	172.2	1.47
Brain and Other Nervous System	78.6	54.9	1.43
Soft Tissue including Heart	33.3	23.4	1.42
Eye and Orbit	10.0	7.2	1.39
Bones and Joints	10.3	7.7	1.34
Miscellaneous	127.1	99.0	1.28
Endocrine System	48.9	116.5	0.42

Table 1: SEER 9 database broad cancer sites of age-adjusted malignant adult cancer incidence rates per 1,000,000 and male to female incidence rate ratios

Childhood Cancer Sites from SEER 9 Database (ICCC3 Recode; 1973-2011)			
Cancer Site	Male Incidence Rate	Female Incidence Rate	Male to Female IRR
Lymphomas and reticuloendothelial neoplasms	19.5	11.5	1.70
Not classified by ICCC or in situ	0.3	0.2	1.50
Hepatic tumors	2.5	1.8	1.39
Leukemias, myeloproliferative & myelodysplastic diseases	47.6	40.0	1.19
CNS and misc intracranial and intraspinal neoplasms	32.7	28.5	1.15
Soft tissue and other extraosseous sarcomas	10.6	9.3	1.14
Malignant bone tumors	6.7	6.1	1.10
Neuroblastoma and other peripheral nervous cell tumors	11.2	10.5	1.07
Retinoblastoma	3.9	4.1	0.95
Renal tumors	7.8	9.0	0.87
Other and unspecified malignant neoplasms	0.4	0.5	0.80
Germ cell & trophoblastic tumors & neoplasms of gonads	4.3	5.6	0.77
Other malignant epithelial neoplasms and melanomas	4.3	7.2	0.60

Table 2: SEER 9 database broad groupings of age-adjusted malignant childhood cancer incidence rates per 1,000,000 and male to female incidence rate ratios

SEER 9 Database (1973-2011) Male to Female Incidence Rate Ratios for 13 Sites Deemed Enigmatic by Edgren, Liang, and Adami (2012)			
Site	Male Incidence Rate	Female Incidence Rate	Male to Female IRR
Tonsil	22.3	6.5	3.43
Nasopharynx	10.2	4.1	2.49
Stomach	131.8	61.1	2.16
Lymphocytic Leukemia	88.7	47.6	1.86
Chronic Myeloid Leukemia	23.5	13.5	1.74
Rectum	137.7	81.6	1.69
Other Non-Epithelial Skin	19.9	12.1	1.64
Myeloma	71.3	47.1	1.51
Acute Myeloid Leukemia	43.4	29.1	1.49
Non-Hodgkin Lymphoma	219.0	147.1	1.49
Small Intestine	20.2	14.1	1.43
Brain and Other Nervous System	78.6	54.9	1.43
Hodgkin Lymphoma	33.9	25.1	1.35
Thyroid	41.4	110.8	0.37

Table 3: Male and female incidence rates (per 1,000,000) and male to female IRRs for the 13 sites deemed to have an enigmatic sex disparity by Edgren and colleagues (2012).

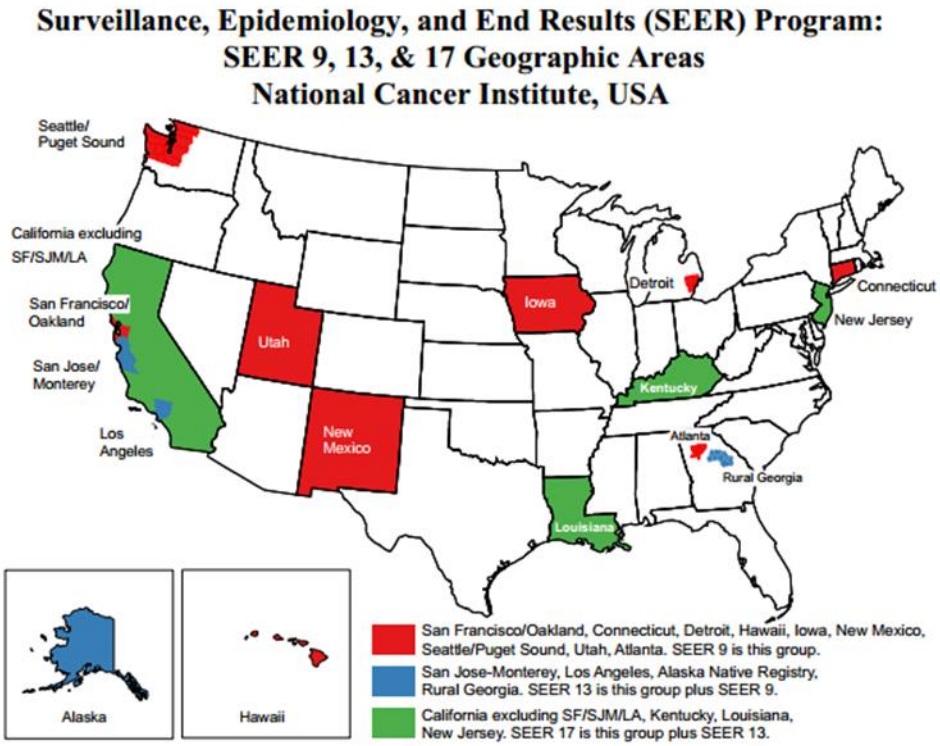

Figure 1: SEER Coverage by Database. SEER 9 coverage in red.

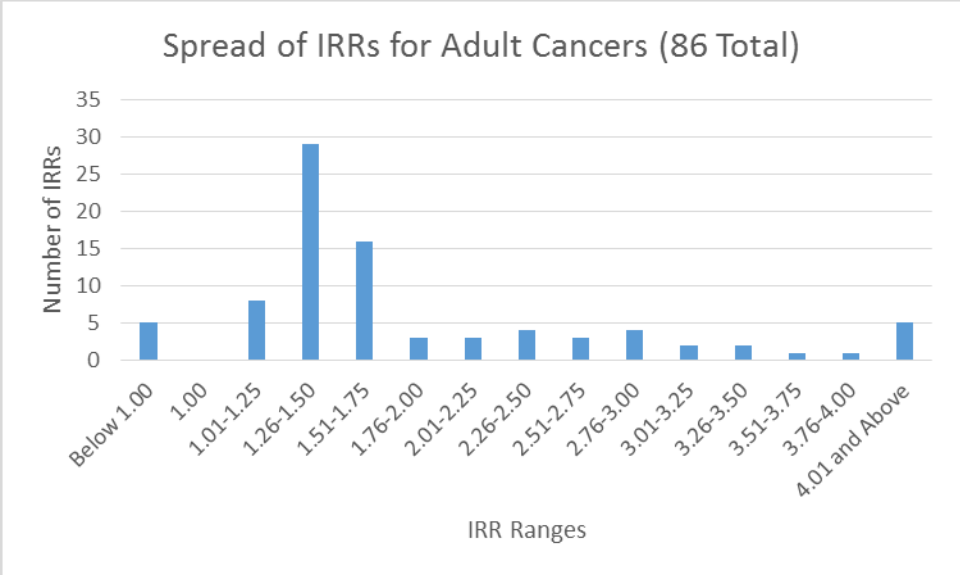

Figure 2: Spread of IRRs for Adult Cancers. Cancer sites below 1.00: Anus, Anal Canal and Anorectum at 0.82; Gallbladder at 0.58; Endocrine System at 0.42; Thyroid at 0.37;

and Peritoneum, Omentum and Mesentery at 0.15. Cancer sites above 4.01: Hypopharynx at 4.18; Mesothelioma at 4.72; Larynx at 5.13; Lip at 6.67; and Kaposi Sarcoma at 27.17.

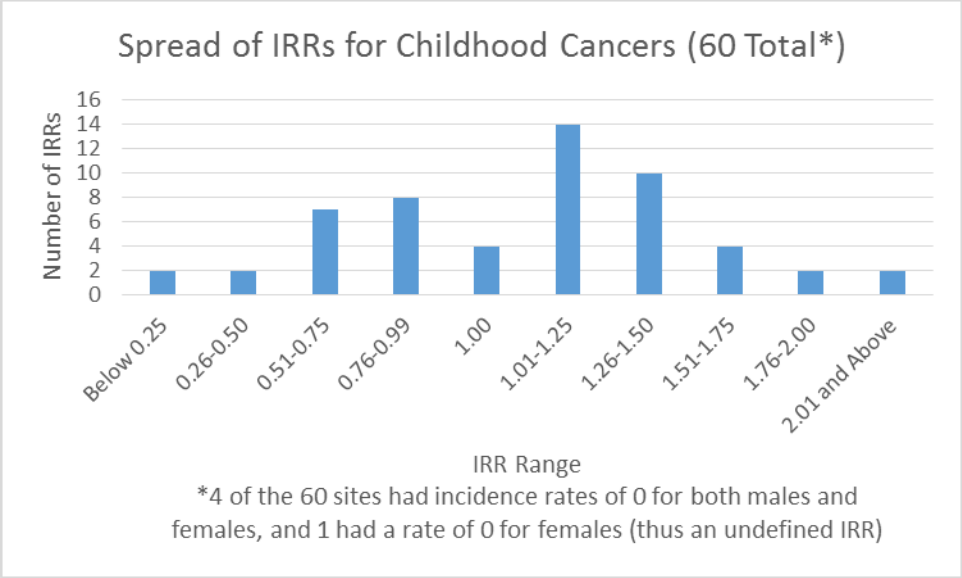

Figure 3: Spread of IRRs for Childhood Cancers. Cancers below 0.25: Gonadal Carcinomas at 0.00 and Other and Unspecified Malignant Gonadal Tumors at 0.00. Cancers above 2.01: Nasopharyngeal Carcinomas at 4.00 and Burkitt Lymphoma at 4.75. The cancer site with an undefined IRR: Myelodysplastic syndrome and other myeloproliferative.