Original Article

موضوع أصيل

SEX AND GENDER BASED DIFFERENCES IN THE INCIDENCE AND SURGICAL MANAGEMENT OF CANCER: A LITERATURE REVIEW

الاختلافات في نسبة الحدوث والمعالجة الجراحية للسرطان على أساس الجنس والنوع الاجتماعي: مراجعة في المنشورات الطبية

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ملخص البحث

هدف البحث: دراسة تأثير الجنس والنوع الاجتماعي على نسب الحدوث والتدبير المعتمد في حالات الأمراض السرطانية.

طرق البحث: تم إجراء تحليل نهائي للمقالات المتضمنة لنسب الحدوث وتدبير الأمراض الخبيثة لدى الكبار والأطفال من خلال البحث في الأدب الطبي في محركي البحث Med Pub New وGoogle في الفترة بين عامي 1985 و2019. تمت دراسة الاختلاف المتعلق بالجنس والنوع في نسب الحدوث، التظاهر السريري، استجابة الأمراض الخبيثة للمعالجة الجراحية والكيميائية والنتائج الملاحظة من خلال نسب البقيا والوفيات. نتج عن البحث 325 مقالاً، وبعد إجراء مراجعة مستقلة يدوياً تم تحديد 197 مقالاً محتملاً تمت دراستها بصورة كاملة وعزل 38 مقالاً منها تم تضمينها في هذه المراجعة، في حيث تم استبعاد المقالات 128 الأخرى.

النتائج: لوحظت اختلافات ناتجة بسبب الجنس والنوع الاجتماعي في نسب حدوث الأمراض السرطانية، التظاهر السريري للحالة، عدوانية الأمراض الخبيثة، نسب البقيا والوفيات لدى الأطفال والكبار. بلغت نسبة حدوث الحالات السرطانية المميتة عند الذكور والإناث: 4 إلى 1 في الجهاز التنفسي، بينما كانت 2 إلى 1 في الجوف الفموي واللسان والمثانة. لوحظ لدى الإناث أن سرطانات الثدي، البريتوان، الثرب المساريقا، الغدة الدرقية، الحويصل الصفراوي، الشرج والقناة الشرجية ومنطقة المستقيم–الشرج أعلى حدوثاً بالمقارنة مع الذكور. لوحظت اختلافات في التظاهر السريري للحالة في الورم الصباغي (الميلانوم)، حيث لوحظ غالباً في الأطراف السفلية عند النساء، بينما لوحظ بشكلٍ أكثر تواردا في الجذع والرأس والرقبة عند الرجال. بلغت نسبة الوفيات السرطانية العامة عند الذكور نسبةً للإناث 1.46 إلى 1. تم ملاحظة فروقات في الاستجابة للمعالجة الكيميائية والتأثيرات الجانبية الملاحظة باختلاف الجنس، حيث سجلت استجابة أفضل للعلاج الكيميائي عند الإناث. أثر التوزع الجغرافي بشكلٍ ملحوظ على نسب وفيات الذكور والإناث في حالات سرطانية معينة كسرطان البنكرياس. لوحظ في حالات سرطانات الطفولة أن إنذار المرض أكثر سوءاً عند الذكور مقارنةً بالإناث، كما أن توزع السرطان يختلف تبعاً والفئة العمرية.

الاستنتاجات: تبين أن الذكور كباراً وأطفالاً أكثر عرضة للإصابة بالسرطان، ولديهم نسبة بقيا إجمالية أسوأ ونسبة وفيات أعلى بالمقارنة مع النساء. ترجع نسب البقيا الأفضل عند النساءِ في عِدّة أنواع من السرطان إلى اختلافاتٍ وراثيةٍ وهرمونيةٍ وتشريحيةٍ. إن الجنس والنوع الاجتماعي ضروري ويجب تضمينه خلال التدبير السريري لحالات السرطان لتسليط الضوء على فهم الفروقات الحيوية بين الذكور والإناث وتجنب الأخطاء التي قد تحدث في التشخيص والتدبير.

ABSTRACT

Objectives: *To study the impact of gender and sex on the incidence and management of malignant diseases.*

Methods: *This meta-analysis study of articles involving incidence and management of malignant cases in both children and adults by searching by New PubMed and Google engine through the literature in*

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the period from 1985 to 2019 inclusive. We studied the disparity related to sex and gender in the incidence, clinical presentation, response to surgical and chemotherapeutic treatment and the outcome in term of survival or mortality of malignant diseases. This search yielded 325 articles, after independent manual review, 197 potential articles were identified and fully reviewed, only 38 articles were included in this study, 128 articles were excluded.

Results: *Gender and sex disparity in the incidence, presentation, aggressiveness, survival, mortality have been clearly noticed for a variety of cancers in both adults and children. The incidence of fatal cases of malignancy, M:F ratio was 4:1 in respiratory tract, while it was 2:1 in oral cavity, tongue and urinary bladder. In females; malignancy of breast, peritoneum, omentum, mesentery, thyroid, gallbladder, anus, anal canal, and anorectum had a higher incidence than in males. Presentation disparity as in melanomas was more commonly noticed on the lower extremities in women while it was more often on the trunk and head and neck in men. Male to female (M:F) cancer mortality rate in general was 1.46:1.0. Sex differences in the response to chemotherapy and their side effects were noticed with an improved response in women. Geographic distribution affects significantly male and female mortality in certain cancers such as pancreatic. In childhood malignancy the prognosis was worse in boys than girls and the distribution of malignancy varies according to age subgroups.*

Conclusions: *Males; adults and children are more prone to develop cancer and have worse overall survival and higher mortality rates than females. The significant survival advantage of women in several different cancer types was due to anatomical, hormonal and genetic differences. Consideration of gender and sex is necessary and should be included in the clinical management of malignant cases to highlight understanding of biological differences between males and females and to avoid mistakes in diagnosis and management.*

INTRODUCTION

The term biologic sex is defined as the developmental differentiations in anatomy and physiology that are a direct consequence of the inherited composition of sex chromosomes (46, XX versus 46, XY karyotypes).[1]

It is the phenotype of sex, or whether an individual is judged to look male or female by others, that evokes a constellation of gendered social expectations, responsibilities and obstacles; such a gendered experience incurs health risks unrelated to chromosomal sex itself.[2] The role played by the environment in cancer susceptibility, is much greater than that of genetics.[3]

The gender disparities in patients with urological cancers could be attributed to smoking habits, occupational risk factors, tumour biology and sex steroid hormones and their receptors. Brannon et al meta-analysis of gene expression showed that, among the total number of genes analyzed in renal clear cell carcinoma, 89% were differentially expressed between genders.[4] Peter considered that alpha and beta naphthylamine, which are secreted into the urine of smokers as initiators or promoters account for 50% and 30% of the bladder, ureter and renal pelvis cancers in men and women respectively.[5]

The skin, being of gender-specific differences that may explain the disparity that men are more vulnerable of developing skin cancers.[6] Ultraviolet exposure and stress induce immunosuppression in the human skin is stronger in males.[7,8]

High-grade colorectal cancer in old age is diagnosed in women more frequently than in men. Men are prone to develop highly malignant cancer in the proximal and distal colon much earlier in life than women.[9]

METHODS

This meta-analysis study of articles involving incidence and management of malignant cases in both children and adults by searching in New PubMed and Google through the literature in the period from 1985 to 2019 inclusive. We studied the disparity related to sex and gender in the clinical presentation, response to surgical and chemotherapeutic treatment and the outcome in term of survival and mortality.

Exclusion criteria were shown in Figure 1. Articles written in languages other than English were not included. This search yielded 325 articles, after independent manual review, 197 potential articles were identified and fully reviewed, only 38 articles were included in this study, 128 articles were excluded.

RESULTS

Gender and sex disparity in the incidence, presentation, aggressiveness, survival, mortality have been clearly noticed for a variety of cancers in both adults and children. Males are more prone to develop cancer, and particularly hematologic malignancies,[10] and they have worse overall survival and higher mortality rates.[11] In childhood malignancy the prognosis was worse in boys than girls.[12]

M:F ratio was 1:150 in breast cancer, 4:6 in colon cancer,1:3 in primary thyroid lymphoma. The incidence of fatal cases of malignancy, M:F ratio was 4:1 in respiratory tract, while it was 2:1 in oral cavity, tongue and urinary bladder, Table 1.

In children, the ratio was 8.5:1.5 in Hodgkin lymphoma. Moreover; the distribution of malignancy varies according to age subgroups that M:F ratios were: 5.3 among (<5 years), 1.4 among (5-9 years), 1.1 among (10-14 years), and 0.8 among (15-19 years), Table 2.

Age	Male-female	Notes	Reference
<5 years	5.3-1	Incidence of childhood cancer	[45]
5-9 years	1.4-1		
10-14 years	1.1-1		
15-19 years	0.8-1		

Table 2. Incidence of childhood cancer age groups.

In females only five cancers had a higher incidence in comparison with males: breast 0.01, peritoneum, omentum, and mesentery 0.18, thyroid 0.39, gallbladder 0.57, and anus, anal canal, and anorectum 0.81.[13]

Mortality rate of cancer in general M:F was 1.46:1. Considering organ specific cancers mortality, M:F ratios were 4.0, 1.35, 1.52 and <1.0 of the urinary

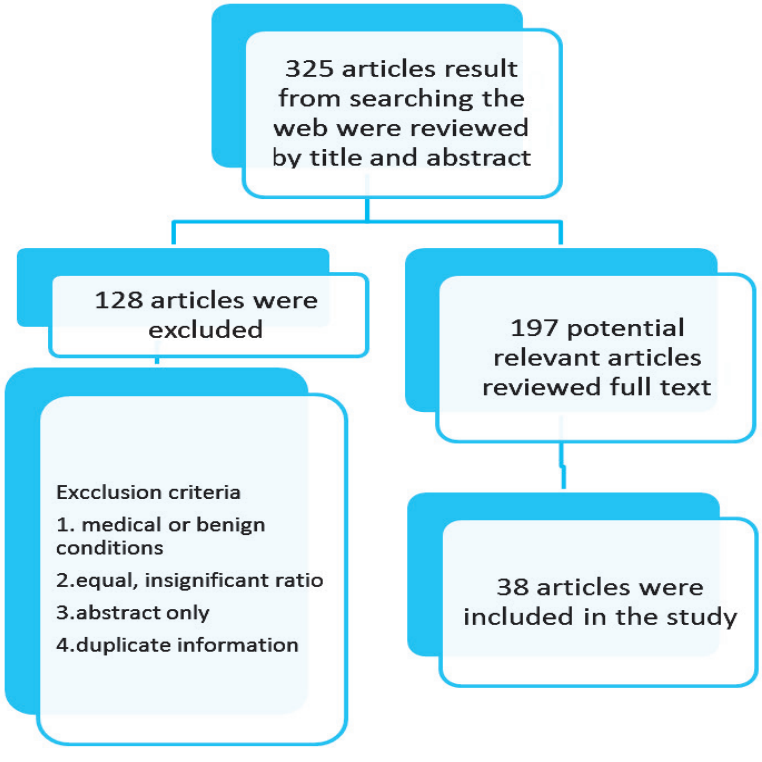

Figure 1. Articles map; collection, selection and exclusion criteria.

Serial No.	Disease	Male-female incidence rate	Notes	Reference
1	Oral cavity	2-1	Fatal cancers	[36]
2	Tongue	2-1		
3	Bladder	2-1		
4	Respiratory tract	4-1		
5	Hodgkin lymphoma	8.5-1.5	In children	[37]
6	Hepatocellular carcinoma	2 to 4:1		[38]
7	Bladder carcinoma	2.7:1		[5]
8	Renal cell carcinoma	2:1 to 3:1		[39]
9	Breast	1-150	Fatal cancers	[36]
	Colon cancer (Excluding rectum)	4-6		
10	Biliary passages	1-(1.5-3)		
11	Thyroid	1-(1.5-3)		
12	Primary thyroid lymphoma	1-3		[40]
13	Breast	1-100		[13]
14	Peritoneum, omentum, and mesentery	1-9		
15	Anus, anal canal, and anorectal	2-9		
16	Thyroid	4-6		[13]
		1-4		[40]
17	Gallbladder	4.5-5.5		[13]
		1-2.3		[41]
18	Esophagus	13.05-29.76		[42]
19	Pancreas	1-1.37		[43]

Table 1. Cancer incidence M-F ratios.

bladder, colorectal cancers, (lung and bronchus), and (gallbladder, anus, and thyroid tumors), respectively, Table 3.

In melanoma, women had a 34% lower risk of death compared with men. The survival rate in melanoma was 50% higher in women compared with men.[14] The M:F five years survival rates of non-small cell lung cancer was 4.95-6.53 in those have undergone thoracotomies with curative intent. Out of 1,242 cases of primary non-small cell lung cancer treated with pulmonary resection, those who were ≥60 years old, women survival rates were 70.4% while men were 50.4%; significantly higher than in the men.[15]

Gender related presentation disparity was noticed, for example, melanomas present more commonly on the lower extremity in women while it was more often on the trunk and head and neck in men, and also incidence of right-sided colon cancer in women was more than men, moreover; it presented with a more aggressive form of this neoplasia.[16,17] Peripheral tumors of primary non-small cell lung cancer treated with pulmonary resection were significantly more common in women than men (71.8% vs. 50.6%, respectively).[15]

David and colleagues studied the distribution of 948 colorectal cancer cases among all seven sub-sites (rectum, recto-sigmoid, sigmoid, descending, transverse, ascending, cecum) comparing males to females. Their found significant decrease in females for recto-sigmoid and sigmoid ($p<0.05$), and significant increase for ascending colon ($p< 0.05$) and cecum ($p<0.01$).[18]

References	[25]	[28]	[13]	[41]	[44]	[42]
In general	1.46 - 1	1.27- 1	1.75-1			
Colorectal cancers	1.35 - 1	-	1.42-1			
Lung and bronchus	1.52 - 1	-	2.36-1			
Urinary bladder	4.0-1					
Gall bladder	1.0<		1-1.78	0.6-1.2		
Esophagus	-	-	4-1			2.28-1
Stomach			2-1			
Pancreas			3-2			
Thyroid tumors	1.0<				0.8-1	

Table 3. Cancer mortality rate M-F ratio.

Severity of disease presentation was also affected by sex as Wolfgang and colleagues stated that at age 70-80 years, about 70% of patients with a high grade cancer were females, and at age of >80 years, all high grade patients were women. By contrast, at age 60 years and younger, the majority of high grade patients were men.[9] Sex differences in the response to chemotherapy and their side effects were noticed with an improved response in women.[19]

DISCUSSION

The disparity in the incidence between male and female of certain cancers may be explained by the known physiological differences. The gendered nature of medicine has significant implications for patients as gender can affect clinical presentation and response to medications in numerous malignant conditions.[20,23]

A higher rate of thyroid cancer in women is linked closely to estrogen which increases the proliferation of human thyroid papillary carcinoma cell line.[24] The lifetime probability of developing cancer is 44.85% for males, and 38.08% for females. The probability is higher for males despite a shorter life expectancy. Other than breast cancer, which rarely occurs in males, only a few cancers are more common in females. Gallbladder, anus, and thyroid tumors consistently show a M:F ratio less than 1.0.[25]

Reduced smoking rates and early detection and treatment of lung cancer in men has decreased mortality during the period from 1991 to 2012. Abrupt decline of mortality due to gastric cancer was recorded in both sexes, in the 1930s in U.S. which was attributed to the control of H. pylori infection, and improving the methods of food preservation.[26] In addition to anatomical and hormonal disparities, genetic differences should be considered when assessing the effects of gender on diseases. Several studies showed the female advantage in several different cancer types. Based on EUROCARE-4 cancer cases, in Europe a significant advantage of women was reported for 16 out of 26 types of cancer.[27]

Maccalli and colleagues reported that melanomas in women -when compared with men- have a lower propensity to metastasize, resulting in a better survival.[17] The higher prevalence of benign thyroid disease and gallbladder stones; risk factors for these cancers can be attributed to the higher incidence of thyroid and gallbladder malignant tumors in women.[10]

Also the female predominance of MALT lymphoma in salivary gland tumors can be explained by the fact that Sjogren's syndrome occurs 90% of the time in females.[28,29]

M:F mortality rates have changed over time for certain cancers; for example, lung and bronchus, larynx, and pancreas cancers had relatively high M:F mortality rates in the 1977 to 1986 period, which consistently decreased with time over the 30-year period. In contrast, the M:F mortality rates consistently increased for several sites between 1977 and 2006, including the esophagus, skin (excluding basal and squamous), liver and intra-hepatic bile duct.[30]

Regarding the effect of geographic distribution, pancreatic cancer mortality varies significantly; in 2018, the mortality of pancreatic cancer in men were the highest in Republic of Moldova (12.3) and Uruguay (12.1), while in women the highest rates were in United Arab Emirates (10.0) and Uruguay (8.1).[31]

Comparing both the mortality rate of cancer in general and organ specific (colorectal, lung and bronchus, gallbladder), the results were compatible in different studies.[25,30]

Yeh and Chen stated that the lower risk of Hepatocellular carcinoma (HCC) in females was due to estrogen, which inhibits IL-6 production which aids progression of HCC in males.[32] Sung et al reported that women appear more prone than men to right-sided colon cancer and this was comparable with both Marshall and Maccalli colleagues.[16,17,33] Weige and colleagues agreed Reeve in reporting that estrogen hormone replacement therapy reduces the incidence of colorectal cancer in post-menopausal women.[8,34,35] David Butcher and colleagues found that the incidence of proximal colon cancer was more frequent in females, and their results were comparable to other studies shown in Table 4.[18]

References	[11]	[46]
Proximal colon	0.78-1	3.7-4.6
Distal colon	0.66-1	2.4-2.1
Rectal cancer	0.56-1	3.2-2.5

Table 4. Incidence of colorectal cancer grouped according to sex, anatomical location M-F ratio.

We found no conflicting results with regard to the M:F ratio in cancer incidence and outcome of surgical and chemotherapeutic management in the studies encountered in our review.

CONCLUSIONS

Males; both children and adults, are more prone to develop cancer, and particularly hematologic malignancies, and have worse overall survival and higher mortality rates. Gender and sex disparity in the incidence, presentation, aggressiveness, survival and mortality have been clearly noticed for a variety of cancers in both adults and children. The incidence in certain cancers in men has been found to be many folds compared to women, (e.g. in breast cancer). Gender related presentation disparity was noticed in melanomas, non-small cell lung and colon cancer.

The significant survival advantage of women in several different cancer types was due to anatomical, hormonal and genetic differences. In Europe, a significant advantage of women was reported for 16 out of 26 types of cancer. Consideration of gender and sex is necessary and should be included in the clinical management of malignant cases to highlight that the biological differences between males and females should included in their management strategy and to avoid mishaps in diagnosis and management of cancer cases.

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