Sex Differences in Cancer-Specific Survival

Subjects: Oncology

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The survival advantage of female patients with cancer is driven by many differential factors, some of which are immune-related. Some sex differences in the immune system persist throughout life, whereas others are most apparent after puberty and before menopause; therefore, both genes and sex hormones are important mediators of immunity-associated cancers. Indeed, sex hormones have numerous effects on the innate and adaptive immune systems—some overlapping and others distinct. Such distinct effects on the immune system can have profound consequences on the differential health of male and female patients.

Keywords: epidemiology ; neoplasms ; SEER program ; sex characteristics ; survival analysis

1. Overview

The life expectancy of women is generally higher than that of men at every age. This dichotomy most likely results from differences in biology, health behaviors, and interactions between the two [1]. These differences are also important in disease and manifest in many ways, including disease presentation, prevalence, and outcomes [2]. For instance, cancer is diagnosed more frequently in men, and men are more likely to die of cancer [3].

Cook *et al*. performed an analysis of data from the Surveillance, Epidemiology, and End Results (SEER) Program (1973–2006) and found that the cancer-specific survival of male patients was lower for most of the 36 sex-nonspecific cancers than for female patients [4]. Micheli *et al*. performed a similar analysis of data from the EUROCARE-4 database and found that the relative survival of female patients was higher for most of the 26 sex-nonspecific cancers than for male patients [5]. These findings were also reproducible in population-based cohorts from other countries, including Sweden, South Korea, Estonia, and Canada [6][7][8][9].

The survival advantage of female patients with cancer is driven by many differential factors, some of which are immune-related. Some sex differences in the immune system persist throughout life, whereas others are most apparent after puberty and before menopause; therefore, both genes and sex hormones are important mediators of immunity-associated cancers [10]. Indeed, sex hormones have numerous effects on the innate and adaptive immune systems—some overlapping and others distinct. Such distinct effects on the immune system can have profound consequences on the differential health of male and female patients [11]. For example, estrogens can suppress oncogenesis but promote autoimmunity, whereas androgens can suppress autoimmunity but promote oncogenesis. Consequently, male and female patients are disproportionately affected by cancers and autoimmune diseases, respectively [11][12].

2. Sex Differences in Cancer

Data regarding sex differences in cancer susceptibility and mortality rates are important because they may be used to identify health behaviors and biological targets that are amenable to interventions. The 5-year all-site cancer-specific survival probability for male adolescents and young adults (AYAs) was 10.4% lower than that for female AYAs, while the all-site hazard of cancer-specific death was 67% higher in male AYAs. We also found that girls had two favorable sites and one unfavorable site, female AYAs had 23 favorable sites and two unfavorable sites, and older adult women had 14 favorable sites and seven unfavorable sites.

Generally, across all ages, the incidence rates of most cancers are higher in male patients than in female patients [13]. In addition, the cancer-specific survival rates of male patients are lower for most cancers [4]. These findings were based on data obtained from the November 2007 submission of SEER 9 (1975–2004) and the November 2008 submission of SEER 17 (1973–2006). The results from other studies of population-based cohorts were similar [5][6][7][8][9]. To glean insights into the role sex hormones play in cancer incidence and survival differences, we stratified our analyses according to the ages of puberty and menopause, in which the levels of sex hormones in female patients are the most markedly different. In general, our results, which were based on data from the November 2019 submission of SEER 18 (2000–2017), also

demonstrated the same trends as those reported in previous studies; however, we found that sex differences in the 5-year all-site cancer-specific survival probabilities and all-site hazard rates for cancer-specific death were the most pronounced in AYAs.

The 5-year all-site cancer-specific survival probabilities we report represent an aggregate measure of the 5-year site-specific cancer-specific survival probabilities weighted by the relative frequencies of the cancers in each site. On the basis of this definition, two independent factors may explain the sex differences we observed in the 5-year all-site cancer-specific survival probabilities in AYAs. First, the relative frequency of aggressive cancers may be higher in male AYAs than in female AYAs. Conversely, the relative frequency of indolent cancers may be higher in female AYAs. Second, the cancer-specific survival probabilities may be lower in male AYAs (and higher in females) for cancers of the same site. Our results show that both factors contribute to these sex differences.

Sex differences in health behaviors may account for the disparity in AYAs. In relation to cancer, health risk behaviors, early detection, psychological adaptation, and social adjustment differ between the sexes. The most notable examples of health risk behaviors are tobacco smoking and alcohol drinking. More men smoke tobacco cigarettes and abuse alcohol than do women. Together, these risk factors are related to 75% of cancers of the oral cavity and pharynx [14]. Indeed, we found that the frequency ratio for cancers of the oral cavity and pharynx was 1.0 between boys and girls, 2.2 between male and female AYAs, and 2.5 between older adult men and women. Interestingly, the corresponding HR values for death caused by cancers of the oral cavity and pharynx were 1.26 (0.72–2.21), 1.36 (1.28–1.44), and 1.01 (0.99–1.03) for children, AYAs, and older adults, respectively; therefore, the hazard of death is higher in male AYAs than in female AYAs, although these sex differences are not present in older adults. These age-related sex differences may be due to biology alone, as well as the interplay between health behaviors and biology. In addition, a working group of the International Agency for Research on Cancer identified sufficient evidence for the contribution of excess body fatness to the risk of 13 cancers, namely cancers of the gastric cardia, colorectum, liver, gallbladder, pancreas, uterine corpus, ovary, and thyroid, as well as esophageal adenocarcinoma, postmenopausal breast cancer, renal cell carcinoma, meningioma, and multiple myeloma [15]. Interestingly, the worldwide age-standardized mean body mass index is higher in women than in men, and the estimates for both sexes have been trending upward historically [16]; therefore, it is not surprising that the estimated proportion of cancers attributable to excess body fatness is twice as high in women 30 years of age or older in the United States [17]. We speculate that sex differences in excess body fatness may account for some differences in site-specific frequencies between the sexes in our study. For example, we found that the male-to-female absolute frequency ratios for cancers of the gallbladder and thyroid—both of which are obesity-related cancers—were 0.4 and 0.2, respectively; however, we could not assess sex differences in body mass index because such data are not collected by SEER.

Most biological sex differences can be attributed to the sex chromosomes. In female patients, some tumor suppressor genes on the lyonized X chromosome escape inactivation. In accordance with the Knudson two-hit hypothesis, Dunford *et al*. showed that the biallelic expression of these genes affords female patients more protection against cancer than that for male patients, which may in part explain the higher incidence rates of cancers in male patients. Interestingly, some genes that do not escape lyonization in healthy cells aberrantly escape lyonization in cancer cells, which may explain sex differences in cancer-specific survival [18]. In male patients, age-related loss of chromosome Y is associated with cancer, while tobacco smoking is associated with reversible mosaic loss of chromosome Y, further highlighting the interplay between health behavior and biology [19][20]. In addition to a higher risk of cancer, mosaic loss of chromosome Y portends reduced survival [21]. Sex differences that affect cancer susceptibility and mortality rates extend to DNA copy number variations, single nucleotide polymorphisms, DNA methylation, mRNA expression, microRNA expression, and protein expression [22][23][24].

In children and young adults, our site-specific analyses revealed many sex differences that were otherwise obfuscated in the all-site analysis. Interestingly, some sex differences reversed from one age group to another. For example, melanoma is more common in female AYAs than in male AYAs; however, melanoma is more common in older adult men than in women. Nevertheless, female patients have better survival probabilities than male patients in both age groups [25]. Site-specific trends are important to fully understand because they may reveal targets for intervention. Indeed, Yuan *et al*. studied 114 clinically actionable genes and found that 60 (>50%) showed sex-biased signatures in seven of eight cancers, suggesting that sex-specific therapeutic strategies are needed for many cancers [23].

3. Conclusions

The all-site survival advantage of female patients with cancer over that of male patients with cancer becomes pronounced during the AYA period, although this difference is mitigated in older adulthood. Site-specific trends in children, AYAs, and older adults are more diverse and warrant individual consideration.

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