Universität Zürich[UZH]

Faculty of Medicine

Factsheet Oncology

Sex and Gender Differences

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Supplementary: Set of slides for the factsheet Oncology

Preliminary note: The factsheet Oncology, like all other factsheets, provides examples of individual gender differences. It does not claim to be a complete representation of the issue. The Commission is aware of the different, subject-specific perspectives on gender/sex. All factsheets were discussed in the Commission Sex and Gender in Medicine of the Faculty of Medicine of the University of Zurich and approved in the following text. Responsibility for the content lies with the authors.

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1.1 Cancer Incidence

Growing evidence shows sex-specific differences in the incidence and mortality associated with various cancers. The three most common cancers in men are prostate, lung, and colorectal cancer, while in women, breast, lung, and colorectal cancer are predominant, at least in the United States. [Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7–30.]

In addition to the incidence of cancer in sexual organs such as prostate and ovary, sex and gender differences in cancers such as colon, lung, and liver have been reported. [Dorak MT, Karpuzoglu E. Gender differences in cancer susceptibility: an inadequately addressed issue. Front Genet. 2012;3:268; Torre LA, Siegel RL, Ward EM, Jemal A. Global cancer incidence and mortality rates and trends--an update. Cancer Epidemiol Biomarkers Prev. 2016;25:16–27.]

Thyroid cancer incidence is much higher in women than in men. [Dorak MT, Karpuzoglu E. Gender differences in cancer susceptibility: an inadequately addressed issue. Front Genet. 2012;3:268.]

Cancer incidence involving colorectal, stomach and liver cancer is higher in men than in women. [Arnold M, Sierra MS, Laversanne M, Soerjomata-ram I, Jemal A, Bray F. Global patterns and trends in colorectal cancer incidence and mortality. Gut. 2017;66:683–69.]

Furthermore, bladder cancer and leukemia have been predominantly diagnosed in men. [Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol. 2017;3:524–548.]

1.2 Cancer Mortality

The mortality of cancer is reported to be greater in men than in women. [Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7–30.]

Especially, lung, colorectal and stomach cancers, which are the leading causes of cancer deaths, show higher mortality in men than in women. [Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7–30; Global, regional, and national cancer incidence, mortality, years of life lost, years lived with disability, and disability-adjusted life-years for 32 cancer groups, 1990 to 2015: a systematic analysis for the global burden of disease study. JAMA Oncol. 2017;3:524–548.]

Women's cancers such as breast, ovarian and uterine corpus cancer result in relatively high mortality. Men-specific cancers such as prostate cancer also represent prominent causes for cancer death. Mortality associated with esophagus, liver, and bladder cancer is higher in men than in women. Men had a 34% higher risk of death due to melanoma compared with women. [EUROCARE-5 Working Group Survival of patients with skin melanoma in Europe increases further: results of the EUROCARE-5 study. Eur J Cancer. 2015;51:2179–2190.]

Therefore, mortality from various cancer types shows gender disparity.

1.3 Lung Cancer

Lung cancer is a major cause of premature and avoidable mortality around the world, and although in more developed countries mortality rates are beginning to decrease, especially in men, the number of deaths from lung cancer in less developed countries is steadily increasing. While historically more men than women have died from lung cancer as a result of higher levels of smoking, the male:female mortality ratio is now showing signs of narrowing. Both sex- and gender-linked factors are important in the etiology of lung cancer. For example, lung cancer is highly associated with tobacco consumption, but also occurs in those who have never smoked. This implies that external factors, such as environmental tobacco smoke (ETS), need consideration; in

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addition, research has suggested that exposure to domestic pollution (e.g. emissions from cooking fuels) and to environmental pollution may also have an impact on lung cancer incidence rates. Of high importance is the incidence of lung cancer in never smokers that is significantly higher in China than in the United States; this is particularly notable in women. These data suggest inclusion of ambient air pollution exposure and gender into lung cancer risk prognostic models to better capture high-risk individuals, especially for non-smoking women. [D. Yang, Cancer Volume 468, 1 January 2020, Pages 82-87: Epidemiology of lung cancer and lung cancer screening programs in China and the United States.]

1.4 Colon Cancer

Colon cancer occurs more frequently in men than in women. [Cai, Y., et al., Sex Differences in Colon Cancer Metabolism Reveal A Novel Subphenotype. Sci Rep, 2020. 10(1): p. 4905.] In total, it arises as the second most common cancer. Colon cancers occur in men predominantly on the left side comprehending the descending colon and the rectum. This allows an easier detection of the cancer in comparison with cancers arising from the right side, which occur more frequently in women. [Kim SE, Paik HY, Yoon H, Lee JE, Kim N, Sung MK. Sex- and gender-specific disparities in colorectal cancer risk. World J Gastroenterol. 2015;21:5167–5175.]

Right-sided colon cancer is associated with a higher severity of cancer compared with left-sided disease [Kim SE, Paik HY, Yoon H, Lee JE, Kim N, Sung MK. Sex- and gender-specific disparities in colorectal cancer risk. World J Gastroenterol. 2015;21:5167–5175.]

Again and again, unfavourable nutrition is cited as a cause of colon cancer. Especially the predominant consumption of foods made from refined flour but also of red meat seems to promote colon cancer. It is undisputed that alcohol contributes to the development of colorectal cancer. New forms of drug and surgical therapy [Brenner, H., M. Kloor, and C. P. Pox, Colorectal cancer. Lancet, 2014. 383 (9927): p. 1490-1502.] have contributed significantly to improving the five-year survival rate which is now quite good, with an average of 40 to 60 percent, but depends crucially on the stage of the disease at which the colorectal cancer is discovered. Therefore, starting from the age of 50 in men and 55 in women in Germany, the cost of a colonoscopy by which pre-stage and early forms can be discovered, is covered by the health insurance funds. [Teoh, D., et al., Excess Cost of Cervical Cancer Screening Beyond Recommended Screening Ages or After Hysterectomy in a Single Institution. J Low Genit Tract Dis, 2018. 22 (3): p. 184-188.]

In gastric cancer, in both sexes, mortality declined rapidly in the 1930s in U.S [Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7–30. doi: 10.3322/caac.21332]. Although the cause of dramatic reduction is not completely understood, the control of Helicobacter pylori infection, and better methods of food preservation resulted in a reduction of mortality due to stomach cancer. [Bertuccio P, Chatenoud L, Levi F, Praud D, Ferlay J, Negri E, Malvezzi M, La Vecchia C. Recent patterns in gastric cancer: a global overview. Int J Cancer. 2009;125:666–67.]

1.5 Genetic and Hormonal Factors

Genetic and molecular disparities between males and females contribute to differences in the incidence of a variety of cancers. Men show a higher incidence of bladder cancer than women. [Siegel RL, Miller KD, Jemal A. Cancer statistics, 2016. CA Cancer J Clin. 2016;66:7–30. doi: 10.3322/caac.21332.]

This is probably related to genetic polymorphism of SULT1A1. Moreover, genetic polymorphism, which is linked to drug metabolizing enzymes, influences the risk of carcinogenesis [Bolufer P, Collado M, Barragán E, Cervera J, Calasanz MJ, Colomer D, Roman-Gómez J, Sanz MA. The potential effect of gender in combination with common genetic polymorphisms of drug-metabolizing enzymes on the risk of developing acute leukemia. Haematologica. 2007;92:308–314.]
An intronic polymorphism of IRF4 gene influences gene transcription in vitro and shows a risk association with childhood acute lymphoblastic leukemia in males. [Biochim Biophys Acta. 2010;1802:292–300.]
Furthermore, sex hormones may contribute to differences in the incidence of cancer between men and women. [Dorak MT, Karpuzoglu E. Gender differences in cancer susceptibility: an inadequately addressed issue.

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Front Genet. 2012;3:268; Do TN, Ucisik-Akkaya E, Davis CF, Morrison BA, Dorak MT.]

1.6 Therapy

Although sex disparities in the incidence and mortality of cancer have been observed for a variety of cancers, chemotherapy has been conducted independent of sex [Keitt SK, Fagan TF, Marts SA. Understanding sex differences in environmental health: a thought leaders' roundtable. Environ Health Perspect. 2004;112:604–609; Becker JB, Arnold AP, Berkley KJ, Blaustein JD, Eckel LA, Hampson E, Herman JP, Marts S, Sadee W, Steiner M, Taylor J, Young E. Strategies and methods for research on sex differences in brain and behavior. Endocrinology. 2005; Yoshioka A, Tanaka S, Hiraoka O, Koyama Y, Hirota Y, Ayusawa D, Seno T, Garrett C, Wataya Y. Deoxyribonucleoside triphosphate imbalance. 5-Fluorodeoxyuridine-induced DNA double strand breaks in mouse FM3A cells and the mechanism of cell death. J Biol Chem. 1987;262:8235–8241.] Research involving animal model and clinical trials has been male-oriented. Accumulating evidence supports sex-related response to chemotherapeutic agents.

Certain cancer therapeutics have stronger side effects in women [1]. Available data clearly demonstrate that women are more susceptible to the toxicity of different types of drugs [2, 3], with an increased risk of acute hematologic and/or nonhematologic toxicity, such as mucositis, nausea and emesis, and alopecia. This has been shown for colorectal [4], small-cell [5], and non–small-cell lung cancers [6]; Hodgkin lymphoma [7]; glioblastoma [8]; Ewing sarcoma [9]; and osteosarcoma [10]. Higher rates of toxicity in the female population are also found in children treated for acute lymphoblastic leukemia [11]. Women are also more vulnerable to late cardiotoxicity after anthracycline treatment in childhood [12]. Men have a higher elimination capacity of various anticancer drugs, including paclitaxel [13], fluorouracil, [Gusella, M., et al., Pharmacokinetic and demographic markers of 5-fluorouracil toxicity in 181 patients on adjuvant therapy for colorectal cancer. Ann Oncol, 2006. 17(11): p. 1656-60.], doxorubicin [14], imatinib [15], sunitinib [16], bevacizumab [17], and rituximab [18]. Given the binding of drugs to erythrocytes, sex differences in hematocrit might also affect drug metabolism [19]. As a result, for many drugs, higher plasma levels are reached in women. Additionally, differences in expression levels of drug metabolizing enzymes resulting from genetic polymorphisms (e.g., cytochrome P450 isoforms; pharmacogenetics) may also play a role [20]. For example, CYP3A, which accounts for the metabolism of approximately 50% of commercially available drugs, has been reported to have a higher activity in women [21]. In contrast, the expression levels of the drug efflux pump P-glycoprotein encoded by the MDR1 gene are higher in men [22].

A number of studies with various chemotherapy regimens have described a positive correlation between female sex, higher response rates, and longer survival [23, 7, 24]. Recommended chemotherapy doses should have the most favorable balance between efficacy and toxicity for the majority of patients. However, these recommended doses are usually established in phase I and II trials with a predominantly male population, that do not consider the potential impact of sex on optimal dosage, and are not designed to identify potentially different optimal doses for both men and women. In fact, the maximum tolerated dose (MTD) for some drugs might actually be lower in women, and administration of standard doses could lead to increased blood drug concentrations and toxicity. In contrast, the lower rates of toxicity in men might be interpreted as a sign of relative underdosing, which could contribute to their poorer prognosis. [Radkiewicz, C., et al., Sex differences in cancer risk and survival: A Swedish cohort study. Eur J Cancer, 2017. 84: p. 130-140.] For chemotherapy, it is generally accepted that a lower dose-intensity has a negative impact on survival, and unintentional underdosing might result in a 10% to 20% relative reduction in survival [25].
Concerning Immunotherapies, the difference in gender plays an important role. The most commonly used immunotherapies are used to activate the immune system from a dormant or suppressed status. Such therapies are called immune-checkpoint inhibitors. As sex plays an important role in immune responses [S. Klein, Nat Rev Immunol 2016], differences have been also detected in patients undergoing immune-checkpoint inhibitors in terms of efficacy and side effects.

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