BIOMOLECULES & THERAPEUTICS

Review
Biomol Ther 26(4), 335-342 (2018)

Sex Differences in Cancer: Epidemiology, Genetics and Therapy

Hae-In Kim†, Hyesol Lim† and Aree Moon*

Duksung Innovative Drug Center, College of Pharmacy, Duksung Women's University, Seoul 01369, Republic of Korea

Abstract

The incidence and mortality of various cancers are associated with sex-specific disparities. Sex differences in cancer epidemiology are one of the most significant findings. Men are more prone to die from cancer, particularly hematological malignancies. Sex difference in cancer incidence is attributed to regulation at the genetic/molecular level and sex hormones such as estrogen. At the genetic/molecular level, gene polymorphism and altered enzymes involving drug metabolism generate differences in cancer incidence between men and women. Sex hormones modulate gene expression in various cancers. Genetic or hormonal differences between men and women determine the effect of chemotherapy. Until today, animal studies and clinical trials investigating chemotherapy showed sex imbalance. Chemotherapy has been used without consideration of sex differences, resulting in disparity of efficacy and toxicity between sexes. Based on accumulating evidence supporting sex differences in chemotherapy, all clinical trials in cancer must incorporate sex differences for a better understanding of biological differences between men and women. In the present review, we summarized the sex differences in (1) incidence and mortality of cancer, (2) genetic and molecular basis of cancer, (3) sex hormones in cancer incidence, and (4) efficacy and toxicity of chemotherapy. This review provides useful information for sex-based chemotherapy and development of personalized therapeutic strategies against cancer.

Key Words: Sex Difference, Cancer, Sex hormone, Chemotherapy

INTRODUCTION

Cancer represents a leading cause of death worldwide (Naghavi *et al*., 2016). Sex plays a crucial role in the incidence, disease prognosis and mortality in a variety of cancers (Siegel *et al*., 2016). The incidence of cancer was about 20% higher in men than in women and the mortality rate was 40% higher in men in the United States from 2009 to 2013 (Siegel *et al*., 2017). Sex differences influence cancer susceptibility at the genetic/molecular levels. Sex hormones also negatively or positively affect the development of various cancers. Biological specificities determine the outcome and response to therapy of cancer.

During the last decades, animal studies and clinical trials used males alone and excluded females (Keitt *et al*., 2004; Becker *et al*., 2005; Zucker and Beery, 2010). Altered sex hormones in the menstrual cycle affect the experimental results (Becker *et al*., 2005). In addition, the 1977 United States Food and Drug Administration guideline excluded women in clinical research due to the risk of birth defects (Merkatz *et al*., 1993). Similar doses were administered to men and women in clinical chemotherapy (Islam *et al*., 2017). Accumulating evidence shows sex-specific differences in toxicity and efficacy of chemotherapy (Tran *et al*., 1998; Rademaker, 2001; Anderson, 2005; Bren, 2005, Schmetzer and Flörcken, 2012). Especially, women experience higher adverse drug reactions to most anticancer drugs than men (Wang and Huang, 2007).

This review summarized studies involving sex differences in epidemiology, sex hormones, and genetic/molecular factors. In addition, we reviewed sex-related differences in chemotherapy using anticancer agents such as 5-fluorouracil (FU), paclitaxel, doxorubicin, cisplatin, bevacizumab and rituximab. This article provides important clues and insights for the precise understanding of sex-specific differences in cancer.

SEX DIFFERENCES IN INCIDENCE AND MORTALITY OF CANCER

Growing evidence shows sex-specific differences in the incidence and mortality associated with various cancers. Prostate, lung, and colorectal cancer occur the most in males,

Open Access **https://doi.org/10.4062/biomolther.2018.103**

Received Jun 1, 2018 **Revised** Jun 6, 2018 **Accepted** Jun 7, 2018
Published Online Jul 1, 2018

***Corresponding Author**
E-mail: armoon@duksung.ac.kr
Tel: +82-2-901-8394, Fax: +82-2-901-8386
†The first two authors contributed equally to this work.

while breast, lung, and colorectal cancer are predominant in females in the United States (Siegel *et al*., 2016). In addition to the incidence of cancer in sex-specific organs such as prostate and ovary, sex differences in cancers such as colon, lung, and liver have been reported (Dorak and Karpuzoglu, 2012; Torre *et al*., 2016). Thyroid cancer incidence is much higher in females than in males (Dorak and Karpuzoglu, 2012). Cancer incidence involving colorectal, stomach and liver cancer is higher in males than in females (Arnold *et al*., 2017). Furthermore, bladder cancer and leukemia have been predominantly diagnosed in males than in females (Fitzmaurice *et al*., 2017). In patients with colorectal cancer, women developed right-sided malignancy while men manifested the disease more on the left side (Kim *et al*., 2015). Right-sided colon cancer is associated with a higher severity of cancer compared with left-sided disease (Kim *et al*., 2015). The cause of disparity in location might be due to differences in estrogen level between men and women.

The mortality of cancer is reported to be greater in men than in women (Siegel *et al*., 2016). Especially, lung, colorectal and stomach cancers, which are the leading causes of cancer deaths, show higher mortality in men than in women (Siegel *et al*., 2016; Fitzmaurice *et al*., 2017). Female cancers such as breast, ovarian and uterine corpus cancer result in relatively high mortality (Siegel *et al*., 2016; Fitzmaurice *et al*., 2017). Men-specific cancers such as prostate cancer also represent prominent causes for cancer death (Siegel *et al*., 2016). Mortality associated with esophagus, liver, and bladder cancer is higher in men than in women (Siegel *et al*., 2016). Men had a 34% higher risk of death due to melanoma compared with women (Crocetti *et al*., 2015). Therefore, mortality from various cancer types shows sex disparity.

Lung cancer was the leading cause of cancer death in men in 20th century due to smoking (Siegel *et al*., 2016). Lung cancer death was decreased by reduced smoking rates and early detection and treatment from 1991 to 2012 (Siegel *et al*., 2016). In both sexes, mortality due to gastric cancer declined rapidly in the 1930s in U.S (Siegel *et al*., 2016). 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 *et al*., 2009; Siegel *et al*., 2016).

SEX DIFFERENCES IN GENETIC AND MOLECULAR BASIS OF CANCER

In genetic and molecular studies, susceptibility to disease varies across the sexes. 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 *et al*., 2016). The lower incidence of bladder cancer in women was correlated with the sulfotransferase 1A1 (SULT1A1) Histidine (His) genotype (Zheng *et al*., 2003). Genetic polymorphism of SULT1A1 showed alteration from Arginine to His, which was triggered by A-to-G transition (Raftogianis *et al*., 1997). It was reported that the His213 allele genotype SULT1A1 significantly decreased the risk of bladder cancer exclusively in women (Zheng *et al*., 2003). Therefore, this gene might be associated with a protective role in women diagnosed with bladder cancer (Dorak and Karpuzoglu, 2012).

Genetic polymorphism, which is linked to drug metabolizing enzymes, influences the risk of carcinogenesis (Bolufer *et al*., 2007). For example, acute leukemia has a higher rate of incidence in men than in women (Bolufer *et al*., 2007). It was reported that men with deletion of glutathione s-methyltransferase T1 (GSTT1), which is a glutathione s-methyltransferase polymorphism, underwent phase 2 metabolism and detected frequently in acute lymphoblastic leukemia (ALL) than men with normal GSTT1 (Mannervik and Danielson, 1988; Hayes and Strange, 2000; Bolufer *et al*., 2007). Deletion of GSTT1 gene abrogated the enzyme activity (Arand *et al*., 1996).

NAD(P)H:quinone oxidoreductase 1 (NQO1) catalyzes free radical detoxification (Traver *et al*., 1992). NQO1 polymorphism with substitution of C to T base pair at position 609 of NQO1 decreases the activity of the enzyme (Asher *et al*., 2002; Fagerholm *et al*., 2008). NQO1 polymorphism showed a higher incidence of ALL only in males, but not in females (Bolufer *et al*., 2007).

Murine double minute 2 (MDM2) downregulates the expression of p53 protein, a tumor suppressor (Eliyahu *et al*., 1989; Bond *et al*., 2004). A single nucleotide polymorphism 309 (SNP 309) in MDM2 promotor increases the affinity of the transcriptional activator Sp1, which enhances the expression of MDM2 and consequently leads to attenuation of p53 pathway (Bond *et al*., 2004). Attenuation of p53 DNA damage response occurs in the presence of both wild-type allele of p53 and G-allele of SNP 309 (Bond *et al*., 2006). In addition, estrogen signaling affects the level of MDM2 (Bond *et al*., 2006). In the diffuse large B-cell lymphoma (DLBCL), sporadic soft-tissue sarcoma, and highly invasive estrogen receptor-positive ductal carcinoma, estrogen signaling pathway increases tumor formation directly or indirectly in women carrying the G-allele of SNP309 (Bond *et al*., 2006). Taken together, genetic and molecular differences might influence the disparity of the risk of cancer between men and women.

SEX DIFFERENCES IN SEX HORMONES IN CANCER INCIDENCE

Sex hormones might contribute to differences in the incidence of cancer between men and women (Do *et al*., 2010; Dorak and Karpuzoglu, 2012). ALL is more likely to occur in men because of limited estrogen level (Do *et al*., 2010). Estrogen plays a role in the inhibition of nuclear factor kappa B (NF-κB). NF-κB regulates the transcription of interferon regulatory factor 4 (IRF4) (Do *et al*., 2010). IRF4 is involved in the differentiation of B and T cells and is overexpressed in B-cell malignancies as a result of NF-κB hyperactivation (Do *et al*., 2010). IRF4 polymorphisms are related with the incidence of ALL (Do *et al*., 2010). Thus, a combination of intronic polymorphism of IRF4 and lack of estrogen might predispose men to leukemia.

Estrogen is linked closely to a higher rate of thyroid cancer development in women (Lee *et al*., 2005; Dorak and Karpuzoglu, 2012). Estrogen increases the proliferation of human thyroid papillary carcinoma cell line and promotes the expression of B-cell lymphoma-extra large (Bcl-XL), which is known as an anti-apoptotic protein (Hsu *et al*., 1997; Lee *et al*., 2005), compared with testosterone. Endogenous female sex hormone such as progestin increase excretion of bile acid, which has been suggested as a potential inducer of colon cancer (McMi-

Table 1. Anticancer drugs with sex differences in efficacy and toxicity

Drug	Sex differences	References
5-fluorouracil	Clearance is higher in males than in females	Milano *et al*., 1992
	Females experienced higher toxicity (including stomatitis, leukopenia, alopecia and diarrhea) frequently and severely than males	Sloan *et al*., 2002
Paclitaxel	Females showed lower elimination than males	Joerger *et al*., 2006
	Peripheral compartment of females is saturated at lower plasma concentrations levels compared with males	Joerger *et al*., 2006
	Elimination is faster in males than in females	Joerger *et al*., 2006
	Females experienced severe leukopenia greater than males	Schmetzer and Flörcken, 2012; Yamamoto *et al*., 2008
	Females showed longer median progression-free survival than males	Yamamoto *et al*., 2008
Doxorubicin	Males have significantly higher clearance than females	Dobbs *et al*., 1995
	Females experienced higher risk of early cardiotoxicity than males following treatment with doxorubicin in childhood leukemia	Lipshultz *et al*., 1995
Cisplatin	Females experienced higher toxicities including vomiting and nausea than males	Liaw *et al*., 2001
	Male rats showed prolonged heat latency and slower motor nerve conduction than female rats	Wongtawatchai *et al*., 2009
	The half-maximal inhibitory concentration (IC_{50}) of male cell lines was lower than that of females	Huang *et al*., 2007
Bevacizumab	Clearance was higher in males than in females	Lu *et al*., 2008
	Female experienced more severe hypertension and neutropenia, and higher rate of abdominal pain than males	Brahmer *et al*., 2011
	Females experienced higher rates of abdominal pain than males	Brahmer *et al*., 2011
Rituximab	Clearance was higher in males than in female	Müller *et al*., 2012
	Half-life of elimination in male was longer compared with females	Müller *et al*., 2012
	The better responses from treatment and outcomes were more prominent in females than in males	Riihijärvi *et al*., 2011
	Male patients had a worse progression-free survival than female patients both in diffuse large B-cell lymphoma and follicular lymphoma	Riihijärvi *et al*., 2011

chael and Potter, 1980; Farhana *et al*., 2016). Exogenous estrogen decreased the production of secondary bile acid which is responsible for promoting malignant change in colonic epithelium (McMichael and Potter, 1980; Everson *et al*., 1991; Grodstein *et al*., 1999). Therefore, female sex hormones may play a protective role in the development of colon cancer, by decreasing the level of bile acid (McMichael and Potter, 1980; Farhana *et al*., 2016).

SEX DIFFERENCES IN EFFICACY AND TOXICITY OF CHEMOTHERAPY

Sex-related differences at the genetic and molecular levels also affect the differences in the degree of drug response (Wang and Huang, 2007). 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 *et al*., 2004; Becker *et al*., 2005; Zucker and Beery, 2010). Research involving animal model and clinical trials has been almost male-oriented. Accumulating evidence supports sex-related response to chemotherapeutic agents. Anticancer drugs, which represent sex differences in efficacy and toxicity, are summarized and listed in Table 1.

5-FU

In the treatment of various cancers, 5-FU has been widely used as an effective chemotherapy (Longley *et al*., 2003). 5-FU as a pyrimidine antagonist inhibits thymidine synthase which is essential for DNA synthesis (Santi *et al*., 1974; Yoshioka *et al*., 1987; Longley *et al*., 2003). It has been observed that 5-FU might elicit different toxicities depending on sex (Stein *et al*., 1995; Sloan *et al*., 2002). Clearance of 5-FU is higher in male (179 l/h/m^2) than in female (155 l/h/m^2) (Milano *et al*., 1992). Low clearance of 5-FU in females can result in higher toxicity (Wang and Huang, 2007). Dihydropyrimidine dehydrogenase (DPD) breaks down 5-FU (Wasternack, 1980; Diasio and Harris, 1989; Longley *et al*., 2003). DPD plays a crucial role in toxicity associated with 5-FU chemotherapy (Harris *et al*., 1991). The activity of DPD was decreased in female and the difference in DPD activity between males and females is 15% (Etienne *et al*., 1994). A lower DPD activity associated with toxicity in women might be attributed to DPD deficiency syndrome (Milano *et al*., 1999). Reduced degradation of 5-FU in female influences therapeutic efficacy and toxicity (Mader, 2007). In 5-FU-based chemotherapy, women experimented higher toxicities, including stomatitis, leukopenia, alopecia, and diarrhea, more frequently and severely than men (Sloan *et al*., 2002).

Paclitaxel

Antitumor effects of paclitaxel, which inhibits depolymerization of cytoskeletal microtubules, interfere with cell division (Schiff and Horwitz, 1980; Jordan and Wilson, 2004). It was reported that female patients with solid tumors have 20% lower elimination of paclitaxel than male patients (Joerger *et al*., 2006). Peripheral compartments of female (0.83 mmol/l) are saturated at lower plasma concentrations compared with those of male (1.74 mmol/l) (Joerger *et al*., 2006). On the other hand, paclitaxel elimination is faster in male (≤0.5 h) than in female (≤1 h) (Joerger *et al*., 2006). In the treatment with paclitaxel combined with carboplatin, the number of female patients exhibiting toxicity such as severe leukopenia was greater than that of male patients (Yamamoto *et al*., 2008; Schmetzer and Flörcken, 2012). Conversely, female patients diagnosed with lung carcinoma (5.3 months) who were treated with paclitaxel combined with carboplatin showed longer median progression-free survival (PFS) rate than male patients (4.4 months) (Yamamoto *et al*., 2008). These sex-related differences might be explained by DNA repair, which was lower in females than in males (Wei *et al*., 2000). The lower DNA repair ability might affect tumor cell in female after administering cytotoxic anticancer drug and influence the prolonged PFS in female patients (Yamamoto *et al*., 2008).

Doxorubicin

Doxorubicin is an anthracycline DNA-damaging agent that targets the topoisomerase 2 activity and DNA intercalation (Gewirtz, 1999; Rivankar, 2014; Mitry and Edwards, 2016). Another predicted mechanism of doxorubicin generates free radicals resulting in damage to membrane and DNA of cancer cell (Gewirtz, 1999; Rivankar, 2014; Mitry and Edwards, 2016). In patients with breast cancer or lymphoma, male with normal liver function showed significantly higher doxorubicin clearance (59 l/h/m^2) than female (27 l/h/m^2) (Dobbs *et al*., 1995). Female might be an independent risk factor increasing the toxicity of doxorubicin such as cardiac abnormalities (Lipshultz *et al*., 1991, 1995). Exposure to doxorubicin in childhood leukemia in females increases the risk of early cardiotoxicity compared with in males (Lipshultz *et al*., 1995). P-glycoprotein, which is expressed by multidrug resistance protein 1 gene, is a drug transporter that pumps many foreign substances out of cells (Schuetz *et al*., 1995). Expression of p-glycoprotein in males is 2-fold higher than in females (Schuetz *et al*., 1995). In females, doxorubicin and doxorubicinol, which is a doxorubicin metabolite, accumulate following a reduced expression of p-glycoprotein and leads to cardiotoxicity (van Asperen *et al*., 1999).

Disparities in drug metabolizing enzymes between men and women might have an impact on drug metabolism or volume of distribution of doxorubicin (Frisancho, 1974; Ley *et al*., 1992; Lipshultz *et al*., 1995). Doxorubicin is not accumulated at a higher concentration in adipose tissue (Rodvold *et al*., 1988, Lipshultz *et al*., 1995). The higher proportion of fat in female patients might lead to a higher concentration of doxorubicin in non-adipose tissues such as heart in women even if men and women carried the same body surface areas.

Cisplatin

Cisplatin as *cis*-diamminedichloroplatinum (II) exhibits covalent bonding with adjacent guanines located in the major groove of DNA (Bellon *et al*., 1991). This intra-strand cross-links with DNA result in distortion of DNA and antitumor effects. Female patients treated with cisplatin-based therapy show substantially higher toxicities such as vomiting and nausea than males (Liaw *et al*., 2001). Male rats treated with cisplatin show general toxicity, prolonged thermal latency and slow motor nerve conduction velocity than female rats (Wongtawatchai *et al*., 2009). Sex-dependent difference may not be related to lower body size in females but physiological variables such as distinct body composition and metabolic activity (Wongtawatchai *et al*., 2009). In the Yoruban population which comprised of African descent, male-derived cell lines demonstrated higher sensitivity to cisplatin than female-derived cell lines (Huang *et al*., 2007). The half-maximal inhibitory concentration (IC_{50}) of cisplatin in male-derived cell lines was lower than that in female-derived cell lines (Huang *et al*., 2007).

Bevacizumab

Bevacizumab is a monoclonal antibody, which blocks vascular endothelial growth factor and inhibits angiogenesis in tumors (Ferrara, 2004; Sandler *et al*., 2006). It was reported that clearance of bevacizumab was 26% higher in male patients with solid tumors than in female patients, which is associated with a greater muscle mass in males than in females (Lu *et al*., 2008). Chemotherapy with bevacizumab for non-small cell lung cancer led to more severe hypertension and neutropenia and higher rate of abdominal pain in female patients than in male patients (Brahmer *et al*., 2011).

Rituximab

Rituximab is a monoclonal antibody, which targets CD20 on B cell surface. It is used to treat autoimmune diseases and hematological cancers such as non-Hodgkin's lymphoma and chronic lymphocytic leukemia. The clearance of rituximab is higher in male patients (8.21 ml/h) with DLBCL than in female patients (12.68 ml/h) and the elimination half-life in male patients ($t_{1/2\beta}$=30.7 days) is longer compared with female patients ($t_{1/2\beta}$=24.7 days) (Müller *et al*., 2012). In the DLBCL treatment with rituximab, the better treatment outcomes were more prominent in females than in males (Riihijärvi *et al*., 2011). GSTT1 deletion might be related to adverse prognosis only in DLBCL male patients who are treated with rituximab (Cho *et al*., 2010). Also, in the treatment with rituximab, male patients had a worse PFS than female patients both in DLBCL and in follicular lymphoma (Riihijärvi *et al*., 2011).

CONCLUSIONS

The present review highlights the importance of sex differences in the epidemiology and chemotherapy of cancer. Evidence supports sex differences in efficacy and toxicity to anticancer drugs based on individual pharmacokinetics and pharmacodynamics. Data suggest that sex influences pathophysiology, clinical signs, treatment outcome and response in cancer. Sex is a crucial factor in predicting chemotherapy outcome, with implications for therapeutic efficacy and toxicity. Our review provides supporting information for appropriate chemotherapy based on sex. Based on the plethora of studies reporting potential sex differences in cancer, cancer research and therapy should be considered specifically to enhance patient outcomes. Sex difference in cancer susceptibility can be used to develop a causal hypothesis for the disease, or to

define subgroups at the highest risk for preventive action. Sex plays a crucial role in improving individual pharmacogenomics and in developing personalized therapeutic medicines. Pharmacogenomic differences between the sexes might play a significant role in chemotherapy in the future. Further studies are needed to provide greater insight into sex differences in cancer and improve treatment outcomes with anticancer agents.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

ACKNOWLEDGMENTS

The present study was supported by the Duksung Women's University Research Grant 2016.

REFERENCES

Anderson, G. D. (2005) Sex and racial differences in pharmacological response: where is the evidence? Pharmacogenetics, pharmacokinetics, and pharmacodynamics. *J. Womens Health (Larchmt)* **14**, 19-29.

Arand, M., Mühlbauer, R., Hengstler, J., Jäger, E., Fuchs, J., Winkler, L. and Oesch, F. (1996) A multiplex polymerase chain reaction protocol for the simultaneous analysis of the glutathione S-transferase GSTM1 and GSTT1 polymorphisms. *Anal. Biochem.* **236**, 184-186.

Arnold, M., Sierra, M. S., Laversanne, M., Soerjomataram, I., Jemal, A. and Bray, F. (2017) Global patterns and trends in colorectal cancer incidence and mortality. *Gut* **66**, 683-691.

Asher, G., Lotem, J., Kama, R., Sachs, L. and Shaul, Y. (2002) NQO1 stabilizes p53 through a distinct pathway. *Proc. Natl. Acad. Sci. U.S.A.* **99**, 3099-3104.

Becker, J. B., Arnold, A. P., Berkley, K. J., Blaustein, J. D., Eckel, L. A., Hampson, E., Herman, J. P., Marts, S., Sadee, W., Steiner, M., Taylor, J. and Young, E. (2005) Strategies and methods for research on sex differences in brain and behavior. *Endocrinology* **146**, 1650-1673.

Bellon, S. F., Coleman, J. H. and Lippard, S. J. (1991) DNA unwinding produced by site-specific intrastrand cross-links of the antitumor drug cis-diamminedichloroplatinum (II). *Biochemistry* **30**, 8026-8035.

Bertuccio, P., Chatenoud, L., Levi, F., Praud, D., Ferlay, J., Negri, E., Malvezzi, M. and La Vecchia, C. (2009) Recent patterns in gastric cancer: a global overview. *Int. J. Cancer* **125**, 666-673.

Bond, G. L., Hu, W., Bond, E. E., Robins, H., Lutzker, S. G., Arva, N. C., Bargonetti, J., Bartel, F., Taubert, H., Wuerl, P., Onel, K., Yip, L., Hwang, S. J., Strong, L. C., Lozano, G. and Levine, A. J. (2004) A single nucleotide polymorphism in the MDM2 promoter attenuates the p53 tumor suppressor pathway and accelerates tumor formation in humans. *Cell* **119**, 591-602.

Bond, G. L., Hirshfield, K. M., Kirchhoff, T., Alexe, G., Bond, E. E., Robins, H., Bartel, F., Taubert, H., Wuerl, P., Hait, W., Toppmeyer, D., Offit, K. and Levine, A. J. (2006) MDM2 SNP309 accelerates tumor formation in a gender-specific and hormone-dependent manner. *Cancer Res.* **66**, 5104-5110.

Bolufer, P., Collado, M., Barragán, E., Cervera, J., Calasanz, M. J., Colomer, D., Roman-Gómez, J. and Sanz, M. A. (2007) The potential effect of gender in combination with common genetic polymorphisms of drug-metabolizing enzymes on the risk of developing acute leukemia. *Haematologica* **92**, 308-314.

Brahmer, J. R., Dahlberg, S. E., Gray, R. J., Schiller, J. H., Perry, M. C., Sandler, A. and Johnson, D. H. (2011) Sex differences in outcome with bevacizumab therapy: analysis of patients with advanced-stage non-small cell lung cancer treated with or without bevacizumab in combination with paclitaxel and carboplatin in the Eastern Cooperative Oncology Group Trial 4599. *J. Thorac. Oncol.* **6**, 103-108.

Bren, L. (2005) Does sex make a difference? *F.D.A. Consum.* **39**, 10-15.

Cho, H. J., Eom, H. S., Kim, H. J., Kim, I. S., Lee, G. W. and Kong, S. Y. (2010) Glutathione-S-transferase genotypes influence the risk of chemotherapy-related toxicities and prognosis in Korean patients with diffuse large B-cell lymphoma. *Cancer Genet. Cytogenet* **198**, 40-46.

Crocetti, E., Mallone, S., Robsahm, T. E., Gavin, A., Agius, D., Ardanaz, E., Lopez, M. C., Innos, K., Minicozzi, P., Borgognoni, L., Pierannunzio, D., Eisemann, N. and EUROCARE-5 Working Group (2015) Survival of patients with skin melanoma in Europe increases further: results of the EUROCARE-5 study. *Eur. J. Cancer* **51**, 2179-2190.

Diasio, R. B. and Harris, B. E. (1989) Clinical pharmacology of 5-fluorouracil. *Clin. Pharmacokinet.* **16**, 215-237.

Do, T. N., Ucisik-Akkaya, E., Davis, C. F., Morrison, B. A. and Dorak, M. T. (2010) 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* **1802**, 292-300.

Dobbs, N. A., Twelves, C. J., Gillies, H., James, C. A., Harper, P. G. and Rubens, R. D. (1995) Gender affects doxorubicin pharmacokinetics in patients with normal liver biochemistry. *Cancer Chemother. Pharmacol.* **36**, 473-476.

Dorak, M. T. and Karpuzoglu, E. (2012) Gender differences in cancer susceptibility: an inadequately addressed issue. *Front Genet.* **3**, 268.

Eliyahu, D., Michalovitz, D., Eliyahu, S., Pinhasi-Kimhi, O. and Oren, M. (1989) Wild-type p53 can inhibit oncogene-mediated focus formation. *Proc. Natl. Acad. Sci. U.S.A.* **86**, 8763-8767.

Etienne, M. C., Lagrange, J. L., Dassonville, O., Fleming, R., Thyss, A., Renée, N., Schneider, M., Demard, F. and Milano, G. (1994) Population study of dihydropyrimidine dehydrogenase in cancer patients. *J. Clin. Oncol.* **12**, 2248-2253.

Everson, G. T., McKinley, C. and Kern, F., Jr. (1991) Mechanisms of gallstone formation in women. Effects of exogenous estrogen (Premarin) and dietary cholesterol on hepatic lipid metabolism. *J. Clin. Invest.* **87**, 237-246.

Fagerholm, R., Hofstetter, B., Tommiska, J., Aaltonen, K., Vrtel, R., Syrjäkoski, K., Kallioniemi, A., Kilpivaara, O., Mannermaa, A., Kosma, V. M., Uusitupa, M., Eskelinen, M., Kataja, V., Aittomäki, K., von Smitten, K., Heikkilä, P., Lukas, J., Holli, K., Bartkova, J., Blomqvist, C., Bartek, J. and Nevanlinna, H. (2008) NAD(P)H:quinone oxidoreductase 1 NQO1*2 genotype (P187S) is a strong prognostic and predictive factor in breast cancer. *Nat. Genet.* **40**, 844-853.

Farhana, L., Nangia-Makker, P., Arbit, E., Shango, K., Sarkar, S., Mahmud, H., Hadden, T., Yu, Y. and Majumdar, A. P. (2016) Bile acid: a potential inducer of colon cancer stem cells. *Stem Cell Res. Ther.* **7**, 181.

Ferrara, N. (2004) Vascular endothelial growth factor: basic science and clinical progress. *Endocr. Rev.* **25**, 581-611.

Fitzmaurice, C., Allen, C., Barber, R. M., Barregard, L., Bhutta, Z. A., Brenner, H., Dicker, D. J., Chimed-Orchir, O., Dandona, R., Dandona, L., Fleming, T., Forouzanfar, M. H., Hancock, J., Hay, R. J., Hunter-Merrill, R., Huynh, C., Hosgood, H. D., Johnson, C. O., Jonas, J. B., Khubchandani, J., Kumar, G. A., Kutz, M., Lan, Q., Larson, H. J., Liang, X., Lim, S. S., Lopez, A. D., MacIntyre, M. F., Marczak, L., Marquez, N., Mokdad, A. H., Pinho, C., Pourmalek, F., Salomon, J. A., Sanabria, J. R., Sandar, L., Sartorius, B., Schwartz, S. M., Shackelford, K. A., Shibuya, K., Stanaway, J., Steiner, C., Sun, J., Takahashi, K., Vollset, S. E., Vos, T., Wagner, J. A., Wang, H., Westerman, R., Zeeb, H., Zoeckler, L., Abd-Allah, F., Ahmed, M. B., Alabed, S., Alam, N. K., Aldhahri, S. F., Alem, G., Alemayohu, M. A., Ali, R., Al-Raddadi, R., Amare, A., Amoako, Y., Artaman, A., Asayesh, H., Atnafu, N., Awasthi, A., Saleem, H. B., Barac, A., Bedi, N., Bensenor. I., Berhane, A., Bernabé, E., Betsu, B., Binagwaho, A., Boneya, D., Campos-Nonato, I., Castañeda-Orjula, C., Catalá-López, F., Chiang, P., Chibueze, C., Chitheer, A., Choi, J. Y., Cowie, B., Damtew, S., das Neves, J., Dey, S., Dharmaratne, S., Dhillon, P., Ding, E., Driscoll, T., Ekwueme, D., Endries, A. Y.,

Farvid, M., Farzadfar, F., Fernandes, J., Fischer, F., G/Hiwot, T. T., Gebru, A., Gopalani, S., Hailu, A., Horino, M., Horita, N., Husseini, A., Huybrechts, I., Inoue, M., Islami, F., Jakovljevic, M., James, S., Javanbakht, M., Jee, S. H., Kasaeian, A., Kedir, M. S., Khader, Y. S., Khang, Y. H., Kim, D., Leigh, J., Linn, S., Lunevicius, R., El Razek, H. M. A., Malekzadeh, R., Malta, D. C., Marcenes, W., Markos, D., Melaku, Y. A., Meles, K. G., Mendoza, W., Mengiste, D. T., Meretoja, T. J., Miller, T. R., Mohammad, K. A., Mohammadi, A., Mohammed, S., Moradi-Lakeh, M., Nagel, G., Nand, D., Le Nguyen, Q., Nolte, S., Ogbo, F. A., Oladimeji, K. E., Oren, E., Pa, M., Park, E. K., Pereira, D. M., Plass, D., Qorbani, M., Radfar, A., Rafay, A., Rahman, M., Rana, S. M., Søreide, K., Satpathy, M., Sawhney, M., Sepanlou, S. G., Shaikh, M. A., She, J., Shiue, I., Shore, H. R., Shrime, M. G., So, S., Soneji, S., Stathopoulou, V., Stroumpoulis, K., Sufiyan, M. B., Sykes, B. L., Tabarés-Seisdedos, R., Tadese, F., Tedla, B. A., Tessema, G. A., Thakur, J. S., Tran, B. X., Ukwaja, K. N., Uzochukwu, B. S. C., Vlassov, V. V., Weiderpass, E., Wubshet Terefe, M., Yebyo, H. G., Yimam, H. H., Yonemoto, N., Younis, M. Z., Yu, C., Zaidi, Z., Zaki, M. E. S., Zenebe, Z. M., Murray, C. J. L. and Naghavi, M. (2017) 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.* **3**, 524-548.

Frisancho, A. R. (1974) Triceps skin fold and upper arm muscle size norms for assessment of nutrition status. *Am. J. Clin. Nutr.* **27**, 1052-1058.

Gewirtz, D. A. (1999) A critical evaluation of the mechanisms of action proposed for the antitumor effects of the anthracycline antibiotics adriamycin and daunorubicin. *Biochem. Pharmacol.* **57**, 727-741.

Grodstein, F., Newcomb, P. A. and Stampfer, M. J. (1999) Postmenopausal hormone therapy and the risk of colorectal cancer: a review and meta-analysis. *Am. J. Med.* **106**, 574-582.

Harris, B. E., Carpenter, J. T. and Diasio, R. B. (1991) Severe 5-fluorouracil toxicity secondary to dihydropyrimidine dehydrogenase deficiency. A potentially more common pharmacogenetic syndrome. *Cancer* **68**, 499-501.

Hayes, J. D. and Strange, R. C. (2000) Glutathione S-transferase polymorphisms and their biological consequences. *Pharmacology* **61**, 154-166.

Hsu, Y. T., Wolter, K. G. and Youle, R. J. (1997) Cytosol-to-membrane redistribution of Bax and Bcl-X(L) during apoptosis. *Proc. Natl. Acad. Sci. U.S.A.* **94**, 3668-3672.

Huang, R. S., Kistner, E. O., Bleibel, W. K., Shukla, S. J. and Dolan, M. E. (2007) Effect of population and gender on chemotherapeutic agent-induced cytotoxicity. *Mol. Cancer Ther.* **6**, 31-36.

Islam, M. M., Iqbal, U., Walther, B. A., Nguyen, P. A., Li, Y. J., Dubey, N. K., Poly, T. N., Masud, J. H. B., Atique, S. and Syed-Abdul, S. (2017) Gender-based personalized pharmacotherapy: a systematic review. *Arch. Gynecol. Obstet.* **295**, 1305-1317.

Joerger, M., Huitema, A. D., van den Bongard, D. H., Schellens, J. H. and Beijnen, J. H. (2006) Quantitative effect of gender, age, liver function, and body size on the population pharmacokinetics of Paclitaxel in patients with solid tumors. *Clin. Cancer. Res.* **12**, 2150-2157.

Jordan, M. A. and Wilson. (2004) Microtubules as a target for anticancer drugs. *Nat. Rev. Cancer* **4**, 253-265.

Keitt, S. K., Fagan, T. F. and Marts, S. A. (2004) Understanding sex differences in environmental health: a thought leaders' roundtable. *Environ. Health Perspect.* **112**, 604-609.

Kim, S. E., Paik, H. Y., Yoon, H., Lee, J. E., Kim, N. and Sung, M. K. (2015) Sex- and gender-specific disparities in colorectal cancer risk. *World J. Gastroenterol.* **21**, 5167-5175.

Lee, M. L., Chen, G. G., Vlantis, A. C., Tse, G. M., Leung, B. C. and van Hasselt, C. A. (2005) Induction of thyroid papillary carcinoma cell proliferation by estrogen is associated with an altered expression of Bcl-xL. *Cancer J.* **11**, 113-121.

Ley, C. J., Lees, B. and Stevenson, J. C. (1992) Sex- and menopause-associated changes in body-fat distribution. *Am. J. Clin. Nutr.* **55**, 950-954.

Liaw, C. C., Wang, C. H., Chang, H. K., Liau, C. T., Yeh, K. Y., Huang, J. S. and Lin, Y. C. (2001) Gender discrepancy observed between chemotherapy-induced emesis and hiccups. *Support Care Cancer* **9**, 435-441.

Lipshultz, S. E., Colan, S. D., Gelber, R. D., Perez-Atayde, A. R., Sallan, S. E. and Sanders, S. P. (1991) Late cardiac effects of doxorubicin therapy for acute lymphoblastic leukemia in childhood. *N. Engl. J. Med.* **324**, 808-815.

Lipshultz, S. E., Lipsitz, S. R., Mone, S. M., Goorin, A. M., Sallan, S. E., Sanders, S. P., Orav, E. J., Gelber, R. D. and Colan, S. D. (1995) Female sex and higher drug dose as risk factors for late cardiotoxic effects of doxorubicin therapy for childhood cancer. *N. Engl. J. Med.* **332**, 1738-1743.

Longley, D. B., Harkin, D. P. and Johnston, P. G. (2003) 5-fluorouracil: mechanisms of action and clinical strategies. *Nat. Rev. Cancer* **3**, 330-338.

Lu, J. F., Bruno, R., Eppler, S., Novotny, W., Lum, B. and Gaudreault, J. (2008) Clinical pharmacokinetics of bevacizumab in patients with solid tumors. *Cancer Chemother. Pharmacol.* **62**, 779-786.

Mader, R. M. (2007) The potential of gender-specific tumor pharmacology. *Pharmacogenomics* **8**, 271-274.

Mannervik, B. and Danielson, U. H. (1988) Glutathione transferases--structure and catalytic activity. *CRC Crit. Rev. Biochem.* **23**, 283-337.

McMichael, A. J. and Potter, J. D. (1980) Reproduction, endogenous and exogenous sex hormones, and colon cancer: a review and hypothesis. *J. Natl. Cancer. Inst.* **65**, 1201-1207.

Merkatz, R. B., Temple, R., Subel, S., Feiden, K. and Kessler, D. A. (1993) Women in clinical trials of new drugs. A change in Food and Drug Administration policy. The working group on women in clinical trials. *N. Engl. J. Med.* **329**, 292-296.

Milano, G., Etienne, M. C., Cassuto-Viguier, E., Thyss, A., Santini, J., Frenay, M., Renee, N., Schneider, M. and Demard, F. (1992) Influence of sex and age on fluorouracil clearance. *J. Clin. Oncol.* **10**, 1171-1175.

Milano, G., Etienne, M. C., Pierrefite, V., Barberi-Heyob, M., Deporte-Fety, R. and Renée, N. (1999) Dihydropyrimidine dehydrogenase deficiency and fluorouracil-related toxicity. *Br. J. Cancer* **79**, 627-630.

Mitry, M. A. and Edwards, J. G. (2016) Doxorubicin induced heart failure: phenotype and molecular mechanisms. *Int. J. Cardiol. Heart Vasc.* **10**,17-24.

Müller, C., Murawski, N., Wiesen, M. H., Held, G., Poeschel, V., Zeynalova, S., Wenger, M., Nickenig, C., Peter, N., Lengfelder, E., Metzner, B., Rixecker, T., Zwick, C., Pfreundschuh, M. and Reiser, M. (2012) The role of sex and weight on rituximab clearance and serum elimination half-life in elderly patients with DLBCL. *Blood* **119**, 3276-3284.

Naghavi, M., Abajobir, A. A., Abbafati, C., Abbas, K. M., Abd-Allah, F., Abera, S. F., Aboyans, V., Adetokunboh, O., Afshin, A., Agrawal, A., Ahmadi, A., Ahmed, M. B., Aichour, A. N., Aichour, M. T. E., Aichour, I., Aiyar, S., Alahdab, F., Al-Aly, Z., Alam, K., Alam, N., Alam, T., Alene, K. A., Al-Eyadhy, A., Ali, S. D., Alizadeh-Navaei, R., Alkaabi, J. M., Alkerwi, A., Alla, F., Allebeck, P., Allen, C., Al-Raddadi, R., Alsharif, U., Altirkawi, K. A., Alvis-Guzman, N., Amare, A. T., Amini, E., Ammar, W., Amoako, Y. A., Anber, N., Andersen, H. H., Andrei, C. L., Androudi, S., Ansari, H., Antonio, C. A. T., Anwari, P., Ärnlöv, J., Arora, M., Artaman, A., Aryal, K. K., Asayesh, H., Asgedom, S. W., Atey, T. M., Avila-Burgos, L., Avokpaho, E. F. G., Awasthi, A., Babalola, T. K., Bacha, U., Balakrishnan, K., Barac, A., Barboza, M. A., Barker-Collo, S. L., Barquera, S., Barregard, L., Barrero, L. H., Baune, B. T., Bedi, N., Beghi, E., Béjot, Y., Bekele, B. B., Bell, M. L., Bennett, J. R., Bensenor, I. M., Berhane, A., Bernabé, E., Betsu, B. D., Beuran, M., Bhatt, S., Biadgilign, S., Bienhoff, K., Bikbov, B., Bisanzio, D., Bourne, R. R. A., Breitborde, N. J. K., Bulto, L. N. B., Bumgarner, B. R., Butt, Z. A., Cahuana-Hurtado, L., Cameron, E., Campuzano, J. C., Car, J., Cárdenas, R., Carrero, J. J., Carter, A., Casey, D. C., Castañeda-Orjuela, C. A., Catalá-López, F., Charlson, F. J., Chibueze, C. E., Chimed-Ochir, O., Chisumpa, V. H., Chitheer, A. A., Christopher, D. J., Ciobanu, L. G., Cirillo, M., Cohen, A. J., Colombara, D., Cooper, C., Cowie, B. C., Criqui, M. H., Dandona, L., Dandona, R., Dargan, P. I., das Neves, J., Davitoiu, D. V., Davletov, K., de Courten, B., Defo, B. K., Degenhardt, L., Deiparine, S., Deribe, K., Deribew, A., Dey, S., Dicker, D., Ding, E.

L., Djalalinia, S., Do, H. P., Doku, D. T., Douwes-Schultz, D., Driscoll, T. R., Dubey, M., Duncan, B. B., Echko, M., El-Khatib, Z. Z., Ellingsen, C. L., Enayati, A., Ermakov, S. P., Erskine, H. E., Eskandarieh, S., Esteghamati, A., Estep, K., Farinha, C. S. E. S., Faro, A., Farzadfar, F., Feigin, V. L., Fereshtehnejad, S. M., Fernandes, J. C., Ferrari, A. J., Feyissa, T. R., Filip, I., Finegold, S., Fischer, F., Fitzmaurice, C., Flaxman, A. D., Foigt, N., Frank, T., Fraser, M., Fullman, N., Fürst, T., Furtado, J. M., Gakidou, E., Garcia-Basteiro, A. L., Gebre, T., Gebregergs, G. B., Gebrehiwot, T. T., Gebremichael, D. Y., Geleijnse, J. M., Genova-Maleras, R., Gesesew, H. A., Gething, P. W., Gillum, R. F., Giref, A. Z., Giroud, M., Giussani, G., Godwin, W. W., Gold, A. L, Goldberg, E. M., Gona, P. N., Gopalani, S. V., Gouda, H. N., Goulart, A. C., Griswold, M., Gupta, R., Gupta, T., Gupta, V., Gupta, P. C., Haagsma, J. A., Hafezi-Nejad, N., Hailu, A. D., Hailu, G. B., Hamadeh, R. R., Hambisa, M. T., Hamidi, S., Hammami, M., Hancock, J., Handal, A. J., Hankey, G. J., Hao, Y., Harb, H. L., Hareri, H. A., Hassanvand, M. S., Havmoeller, R., Hay, S. I., He, F., Hedayati, M. T., Henry, N. J., Heredia-Pi, I. B., Herteliu, C., Hoek, H. W., Horino, M., Horita, N., Hosgood, H. D., Hostiuc, S., Hotez, P. J., Hoy, D. G., Huynh, C., Iburg, K. M., Ikeda, C., Ileanu, B. V., Irenso, A. A., Irvine, C. M. S., Islam, S. M. S., Jacobsen, K. H., Jahanmehr, N., Jakovljevic, M. B., Javanbakht, M., Jayaraman, S. P., Jeemon, P., Jha, V., John, D., Johnson, C. O., Johnson, S. C., Jonas, J. B., Jürisson, M., Kabir, Z., Kadel, R., Kahsay, A., Kamal, R., Karch, A., Karimi, S. M., Karimkhani, C., Kasaeian, A., Kassaw, N. A., Kassebaum, N. J., Katikireddi, S. V., Kawakami, N., Keiyoro, P. N., Kemmer, L., Kesavachandran, C. N., Khader, Y. S., Khan, E. A., Khang, Y. H., Khoja, A. T. A., Khosravi, M. H., Khosravi, A., Khubchandani, J., Kiadaliri, A. A., Kieling, C., Kievlan, D., Kim, Y. J., Kim, D., Kimokoti, R. W., Kinfu, Y., Kissoon, N., Kivimaki, M., Knudsen, A. K., Kopec, J. A., Kosen, S., Koul, P. A., Koyanagi, A., Kulikoff, X. R., Kumar, G. A., Kumar, P., Kutz, M., Kyu, H. H., Lal, D. K., Lalloo, R., Lambert, T. L. N., Lan, Q., Lansingh, V. C., Larsson, A., Lee, P. H., Leigh, J., Leung, J., Levi, M., Li, Y., Li Kappe, D., Liang, X., Liben, M. L., Lim, S. S., Liu, P. Y., Liu, A., Liu, Y., Lodha, R., Logroscino, G., Lorkowski, S., Lotufo, P. A., Lozano, R., Lucas, T. C. D., Ma, S., Macarayan, E. R. K., Maddison, E. R., Magdy Abd El Razek, M., Majdan, M., Majdzadeh, R., Majeed, A., Malekzadeh, R., Malhotra, R., Malta, D. C., Manguerra, H., Manyazewal, T., Mapoma, C. C., Marczak, L. B., Markos, D., Martinez-Raga, J., Martins-Melo, F. R., Martopullo, I., McAlinden, C., McGaughey, M., McGrath, J. J., Mehata, S., Meier, T., Meles, K. G., Memiah, P., Memish, Z. A., Mengesha, M. M., Mengistu, D. T., Menota, B. G., Mensah, G. A., Meretoja, T. J., Meretoja, A., Millear, A., Miller, T. R., Minnig, S., Mirarefin, M., Mirrakhimov, E. M., Misganaw, A., Mishra, S. R., Mohamed, I. A., Mohammad, K. A., Mohammadi, A., Mohammed, S., Mokdad, A. H., Mola, G. L. D., Mollenkopf, S. K., Molokhia, M., Monasta, L., Montañez, J. C., Montico, M., Mooney, M. D., Moradi-Lakeh, M., Moraga, P., Morawska, L., Morozoff, C., Morrison, S. D., Mountjoy-Venning, C., Mruts, K. B., Muller, K., Murthy, G. V. S., Musa, K. I., Nachega, J. B., Naheed, A., Naldi, L., Nangia, V., Nascimento, B. R., Nasher, J. T., Natarajan, G., Negoi, I., Ngunjiri, J. W., Nguyen, C. T., Nguyen, Q. L., Nguyen, T. H., Nguyen, G., Nguyen, M., Nichols, E., Ningrum, D. N. A., Nong, V. M., Noubiap, J. J. N., Ogbo, F. A., Oh, I. H., Okoro, A., Olagunju, A. T., Olsen, H. E., Olusanya, B. O., Olusanya, J. O., Ong, K., Opio, J. N., Oren, E., Ortiz, A., Osman, M., Ota, E., Pa, M., Pacella, R. E., Pakhale, S., Pana, A., Panda, B. K., Panda-Jonas, S., Papachristou, C., Park, E. K., Patten, S. B., Patton, G. C., Paudel, D., Paulson, K., Pereira, D. M., Perez-Ruiz, F., Perico, N., Pervaiz, A., Petzold, M., Phillips, M. R., Pigott, D. M., Pinho, C., Plass, D., Pletcher, M. A., Polinder, S., Postma, M. J., Pourmalek, F., Purcell, C., Qorbani, M., Quintanilla, B. P. A., Radfar, A., Rafay, A., Rahimi-Movaghar, V., Rahman, M. H. U., Rahman, M., Rai, R. K., Ranabhat, C. L., Rankin, Z., Rao, P. C., Rath, G. K., Rawaf, S., Ray, S. E., Rehm, J., Reiner, R. C., Reitsma, M. B., Remuzzi, G., Rezaei, S., Rezai, M. S., Rokni, M. B., Ronfani, L., Roshandel, G., Roth, G. A., Rothenbacher, D., Ruhago, G. M., Sa, R., Saadat, S., Sachdev, P. S., Sadat, N., Safdarian, M., Safi, S., Safiri, S., Sagar, R., Sahathevan, R., Salama, J., Salamati, P., Salomon, J. A., Samy, A. M., Sanabria, J. R., Sanchez-Niño, M. D., Santomauro, D., Santos, I. S., Santric Milicevic, M. M., Sartorius, B., Satpathy, M., Schmidt, M. I., Schneider, I. J. C., Schulhofer-Wohl, S., Schutte, A. E., Schwebel, D. C., Schwendicke, F., Sepanlou, S. G., Servan-Mori, E. E., Shackelford, K. A., Shahraz, S., Shaikh, M. A., Shamsipour, M., Shamsizadeh, M., Sharma, J., Sharma, R., She, J., Sheikhbahaei, S., Shey, M., Shi, P., Shields, C., Shigematsu, M., Shiri, R., Shirude, S., Shiue, I., Shoman, H., Shrime, M. G., Sigfusdottir, I. D., Silpakit, N., Silva, J. P., Singh, J. A., Singh, A., Skiadaresi, E., Sligar, A., Smith, D. L., Smith, A., Smith, M., Sobaih, B. H. A., Soneji, S., Sorensen, R. J. D., Soriano, J. B., Sreeramareddy, C. T., Srinivasan, V., Stanaway, J. D., Stathopoulou, V., Steel, N., Stein, D. J., Steiner, C., Steinke, S., Stokes, M. A., Strong, M., Strub, B., Subart, M., Sufiyan, M. B., Sunguya, B. F., Sur, P. J., Swaminathan, S., Sykes, B. L., Tabarés-Seisdedos, R., Tadakamadla, S. K., Takahashi, K., Takala, J. S., Talongwa, R. T., Tarawneh, M. R., Tavakkoli, M., Taveira, N., Tegegne, T. K., Tehrani-Banihashemi, A., Temsah, M. H., Terkawi, A. S., Thakur, J. S., Thamsuwan, O., Thankappan, K. R., Thomas, K. E., Thompson, A. H., Thomson, A. J., Thrift, A. G., Tobe-Gai, R., Topor-Madry, R., Torre, A., Tortajada, M., Towbin, J. A., Tran, B. X., Troeger, C., Truelsen, T., Tsoi, D., Tuzcu, E. M., Tyrovolas, S., Ukwaja, K. N., Undurraga, E. A., Updike, R., Uthman, O. A., Uzochukwu, B. S. C., van Boven, J. F. M., Vasankari, T., Venketasubramanian, N., Violante, F. S., Vlassov, V. V., Vollset, S. E., Vos, T., Wakayo, T., Wallin, M. T., Wang, Y. P., Weiderpass, E., Weintraub, R. G., Weiss, D. J., Werdecker, A., Westerman, R., Whetter, B., Whiteford, H. A., Wijeratne, T., Wiysonge, C. S., Woldeyes, B. G., Wolfe, C. D. A., Woodbrook, R., Workicho, A., Xavier, D., Xiao, Q., Xu, G., Yaghoubi, M., Yakob, B., Yano, Y., Yaseri, M., Yimam, H. H., Yonemoto, N., Yoon, S. J., Yotebieng, M., Younis, M. Z., Zaidi, Z., Zaki, M. E. S., Zegeye, E. A., Zenebe, Z. M., Zerfu, T. A., Zhang, A. L., Zhang, X., Zipkin, B., Zodpey, S., Lopez, A. D. and Murray, C. J. L. (2017) Global, regional, and national age-sex specific mortality for 264 causes of death, 1980-2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet* **390**, 1151-1210.

Rademaker, M. (2001) Do women have more adverse drug reactions? *Am. J. Clin. Dermatol.* **2**, 349-351.

Raftogianis, R. B., Wood, T. C., Otterness, D. M., Van Loon, J. A. and Weinshilboum, R. M. (1997) Phenol sulfotransferase pharmacogenetics in humans: association of common SULT1A1 alleles with TS PST phenotype. *Biochem. Biophys. Res. Commun.* **239**, 298-304.

Riihijärvi, S., Taskinen, M., Jerkeman, M. and Leppä, S. (2011) Male gender is an adverse prognostic factor in B-cell lymphoma patients treated with immunochemotherapy. *Eur. J. Haematol.* **86**, 124-128.

Rivankar, S. (2014) An overview of doxorubicin formulations in cancer therapy. *J. Cancer Res. Ther.* **10**, 853-858.

Rodvold, K. A., Rushing, D. A. and Tewksbury, D. A. (1988) Doxorubicin clearance in the obese. *J. Clin. Oncol.* **6**, 1321-1327.

Sandler, A., Gray, R., Perry, M. C., Brahmer, J., Schiller, J. H., Dowlati, A., Lilenbaum, R. and Johnson, D. H. (2006) Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. *N. Engl. J. Med.* **355**, 2542-2550.

Santi, D. V., McHenry, C. S. and Sommer, H. (1974) Mechanism of interaction of thymidylate synthetase with 5-fluorodeoxyuridylate. *Biochemistry* **13**, 471-481.

Schiff, P. B. and Horwitz, S. B. (1980) Taxol stabilizes microtubules in mouse fibroblast cells. *Proc. Natl. Acad. Sci. U.S.A.* **77**, 1561-1565.

Schmetzer, O. and Flörcken, A. (2012) Sex differences in the drug therapy for oncologic diseases. In Sex and Gender Differences in Pharmacology (V. Regitz-Zagrosek, Ed.), pp. 411-442. Springer, Germany.

Schuetz, E. G., Furuya, K. N. and Schuetz, J. D. (1995) Interindividual variation in expression of P-glycoprotein in normal human liver and secondary hepatic neoplasms. *J. Pharmacol. Exp. Ther.* **275**, 1011-1018.

Siegel, R. L., Miller, K. D. and Jemal, A. (2016) Cancer statistics, 2016. *CA Cancer J. Clin.* **66**, 7-30

Siegel, R. L., Miller, K. D. and Jemal, A. (2017) Cancer statistics, 2017. *CA Cancer J. Clin.* **67**, 7-30.

Sloan, J. A., Goldberg, R. M., Sargent, D. J., Vargas-Chanes, D., Nair, S., Cha, S. S., Novotny, P. J., Poon, M. A., O'Connell, M. J. and Loprinzi, C. L. (2002) Women experience greater toxicity with fluorouracil-based chemotherapy for colorectal cancer. *J. Clin. Oncol.*

20, 1491-1498.
Stein, B. N., Petrelli, N. J., Douglass, H. O., Driscoll, D. L., Arcangeli, G. and Meropol, N. J. (1995) Age and sex are independent predictors of 5-fluorouracil toxicity. Analysis of a large scale phase III trial. *Cancer* **75**, 11-17.
Torre, L. A., Siegel, R. L., Ward, E. M. and Jemal, A. (2016) Global cancer incidence and mortality rates and trends--an update. *Cancer Epidemiol. Biomarkers Prev.* **25**, 16-27.
Tran, C., Knowles, S. R., Liu, B. A. and Shear, N. H. (1998) Gender differences in adverse drug reactions. *J. Clin. Pharmacol.* **38**, 1003-1009.
Traver, R. D., Horikoshi, T., Danenberg, K. D., Stadlbauer, T. H., Danenberg, P. V., Ross, D. and Gibson, N. W. (1992) NAD(P)H:quinone oxidoreductase gene expression in human colon carcinoma cells: characterization of a mutation which modulates DT-diaphorase activity and mitomycin sensitivity. *Cancer Res.* **52**, 797-802.
van Asperen, J., van Tellingen, O., Tijssen, F., Schinkel, A. H. and Beijnen, J. H. (1999) Increased accumulation of doxorubicin and doxorubicinol in cardiac tissue of mice lacking mdr1a P-glycoprotein. *Br. J. Cancer* **79**, 108-113.
Wang, J. and Huang, Y. (2007) Pharmacogenomics of sex difference in chemotherapeutic toxicity. *Curr. Drug Discov. Technol.* **4**, 59-68.
Wasternack, C. (1980) Degradation of pyrimidines and pyrimidine analogs--pathways and mutual influences. *Pharmacol. Ther.* **8**, 629-651.
Wei, Q., Cheng, L., Amos, C. I., Wang, L. E., Guo, Z., Hong, W. K. and Spitz, M. R. (2000) Repair of tobacco carcinogen-induced DNA adducts and lung cancer risk: a molecular epidemiologic study. *J. Natl. Cancer Inst.* **92**, 1764-1772.
Wongtawatchai, T., Agthong, S., Kaewsema, A. and Chentanez, V. (2009) Sex-related differences in cisplatin-induced neuropathy in rats. *J. Med. Assoc. Thai.* **92**, 1485-1491.
Yamamoto, H., Sekine, I., Yamada, K., Nokihara, H., Yamamoto, N., Kunitoh, H., Ohe, Y. and Tamura, T. (2008) Gender differences in treatment outcomes among patients with non-small cell lung cancer given a combination of carboplatin and paclitaxel. *Oncology* **75**, 169-174.
Yoshioka, A., Tanaka, S., Hiraoka, O., Koyama, Y., Hirota, Y., Ayusawa, D., Seno, T., Garrett, C. and Wataya, Y. (1987) Deoxyribonucleoside triphosphate imbalance. 5-Fluorodeoxyuridine-induced DNA double strand breaks in mouse FM3A cells and the mechanism of cell death. *J. Biol. Chem.* **262**, 8235-8241.
Zheng, L., Wang, Y., Schabath, M. B., Grossman, H. B. and Wu, X. (2003) Sulfotransferase 1A1 (SULT1A1) polymorphism and bladder cancer risk: a case-control study. *Cancer Lett.* **202**, 61-69.
Zucker, I. and Beery, A. K. (2010) Males still dominate animal studies. *Nature* **465**, 690.