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Gender and sex disparity in cancer trials

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ABSTRACT

The study population within phase III clinical trials leading to approval of new cancer agents should ideally more closely mirror the population who will ultimately receive these agents. Although the number of females participating in clinical trials has increased over the past several decades, females are still under-represented in preclinical studies, in early phase clinical trials and even in some later phase cancer clinical trials. In the USA, this is particularly true for women from minority populations and elderly women. In this review, we review gender and sex disparities in cancer trials, the reasons for these disparities, the barriers to clinical trial enrolment and ways to improve diversity in cancer clinical trials.

INTRODUCTION

Both gender and sex are important determinants of health.[1] Gender (eg, woman, man) comprises the social, environmental, cultural and behavioural factors and choices that influence a person's self-identity and health, rather than biological sex (eg, female, male).[2] Although the number of females participating in clinical trials has increased over the past several decades, females are still under-represented in preclinical studies, early phase clinical trials and in some later phase cancer studies.[3 4] This article will primarily focus on gender and sex inequality as it pertains to women and females, particularly in cancer studies. Between May 2020 and June 2020, we searched PubMed.gov for available literature using search terms 'clinical trials', 'sex', 'gender', 'disparity', 'accrual', 'regulatory', 'cancer' and 'barriers'. We also searched websites for the US Food and Drug Administration (FDA), European Medicines Agency (EMA) and Health Canada for these terms.

INFLUENCE OF SEX AND GENDER ON DRUG TOXICITY AND OUTCOMES IN CANCER PATIENTS

When trial populations do not mirror the incidence of disease, the reproducibility and generalisability of results are limited. Clinical trial data generated in men does not necessarily extrapolate to women. Women have a 1.5-fold to 1.7-fold greater risk of developing an adverse reaction to a drug.[5] In 2001, the US General Accounting Office (GAO, subsequently renamed the General Accountability Office) reported that 8 of the 10 prescription drugs withdrawn from the US market between January 1997 and January 2001 posed greater risks for women than men.[6] A large pooled analysis of 4 randomised clinical trials in oesophagogastric cancer demonstrated that (after adjusting for potential confounding factors) females are at greater risk for experiencing grade 3 or higher gastrointestinal toxicity, had a significantly higher incidence of serious adverse events on treatment and received comparatively less cycles of chemotherapy overall than males.[7] Other studies have demonstrated higher rates of haematological and non-haematological toxicities such as mucositis and alopecia in colorectal cancer, small-cell and non-small cell lung cancers (NSCLC), Hodgkin's lymphoma, Ewing sarcoma and osteosarcoma.[8] In newly diagnosed glioblastoma, female sex is a predictor for severe myelotoxicity from temozolomide.[9]

In addition, sex contributes to differences in cancer risk according to tumour types (even after controlling for known epidemiological risk factors) and to differences in treatment response.[8 10] A meta-analysis of 20 randomised controlled trials of immune checkpoint inhibitors for the treatment of a variety of solid tumours (mostly melanoma and NSCLC) demonstrated that the pooled reduction of risk of death was double the size for male patients than for female patients.[11] The mechanisms for these differences are not fully understood although sex influences a variety of factors including anatomy and physiology, immune responses and variability in pharmacokinetics and pharmacodynamics.[8 10] Analysis of The Cancer Genome Atlas (TCGA) studies demonstrates differences in somatic mutation load and genomic instability between females and males.[12] Additional gender-specific aspects of the epidemiology, molecular genetics and outcomes of cancers including chronic lymphocytic leukaemia, lung cancer, gastrointestinal cancer and primary brain tumours are discussed in other articles within this special issue.

REGULATORY POLICIES REGARDING WOMEN IN CLINICAL TRIALS

In the USA, the perception that women needed to be protected from harm in clinical

research rose out of the sad legacy of thalidomide (a sedative given to pregnant women to prevent morning sickness that caused birth defects) and diethylstilbestrol (a synthetic oestrogen prescribed to pregnant women to prevent miscarriages that increased the risk of cervical and vaginal clear cell adenocarcinoma, among other risks, in their exposed daughters).[13] The 1977 US FDA guideline *General Considerations for Clinical Evaluation of Drugs* advised the exclusion of women of childbearing potential (WCBP) from early dose-ranging studies.[14] Although the guidance document did specify inclusion of WCBP in studies after sufficient safety data was established, the guidance was misinterpreted to mean exclusion of women from all clinical trials and thus contributed to the gender disparity in clinical trials.[13] Recognising the need and bolstered by advocacy groups supporting the study of women's health, the US National Institutes of Health (NIH) established a policy in 1986 to encourage the inclusion of women in studies.[15] However, an investigation by the GAO in 1990 revealed that women were still routinely excluded from medical research studies supported by federal funds.[16] The NIH Revitalization Act of 1993 directed the NIH to provide guidelines for greater inclusion of women and minority participants in clinical research.[17] The same year, the FDA published their *Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs*[18] which reversed the 1977 FDA guideline excluding WCBP from participating in early phase drug studies. The new guidance endorsed representative inclusion of women in phase 1, 2 and 3 trials as well as analysis of data on sex differences. Similarly, in 1997, Health Canada released the *Guidance Document on the Inclusion of Women in Clinical Trials* recommending appropriate inclusion of women in all phases of clinical trials.[19]

By the early 2000s, these policies appeared to be making an impact on increasing female participation in clinical trials. In 2001, the GAO reported that women represented 52% of the study participants in all of the new drug applications labelled for use in both men and women (not limited to cancer indications) between 1998 and 2000.[20] However, women were only 22% of the participants in the initial, small scale safety trials which provide important information about safety and help determine dosing for later trials. In their 2005 report, the EMA concluded that women were slightly under-represented in phase 1 and phase 2 trials but not phase 3[21] and thus argued against the need for a separate guideline on women as a special population. However, given the aforementioned sex differences in toxicity and pharmacokinetics, the relative under-representation of women in early phase trials may have serious consequences.[22]

The 2001 GAO report additionally found that that the FDA had not effectively overseen the presentation and analysis of data related to sex differences in drug development.[20] The influence of sex or gender is not widely analysed and not often reported in studies.[3] Most preclinical data is performed on male animals and cells, and analysis of preclinical data by sex remains inadequate.[23]

Guidelines promoting consideration of sex and gender in clinical trials were further expanded in Canada, the European Union (EU) and the USA. In 2013, Health Canada issued its updated version of *Considerations for Inclusion of Women in Clinical Trials and Analysis of Data by Sex*.[24] This guidance document advises researchers to analyse sex differences across the product life cycle. The *EU Clinical Trial Regulation No 536/2014* harmonised clinical trial requirements throughout the EU by establishing a new clinical trials information system, promoting increased clinical trial data transparency.[25] The regulation also states that "the subjects participating in a clinical trial should represent the population groups, for example, gender and age groups, that are likely to use the medicinal product investigated in the clinical trial". In 2014, NIH announced a change in research policy, calling for balancing of sex in animal and human studies.[26] As of January 2016, the NIH expects that sex as a biological variable (SABV) will be factored into research designs, analyses and reporting in vertebrate animal and human studies.[27] Other funding mechanisms including the European Commission and the Canadian Institutes of Health Research also encourage researchers to integrate sex and gender in the whole research process.[28] Many journals are also requiring more transparency and rigour in reporting SABV.[2 28]

GENDER-BASED DISPARITIES IN CANCER CLINICAL TRIAL ENROLMENT

Even though gender-based disparities are improving in human studies in general, women are still under-represented in cancer trials.[29] Of the 5157 patients who participated in oncology trials that led to the FDA approval of 17 new drugs in 2018, only 38% were women.[30] When examining US National Cancer Institute (NCI) sponsored clinical trials, women were less likely to be enrolled in studies of colorectal cancer,[31] lung cancer[31] and surgical oncology.[32] In another study based on enrolment data from all therapeutic trials reported as completed in ClinicalTrials.gov from 2003 to 2016 (excluding prostate cancer and breast cancer), females were under-represented in lung cancer, melanoma and pancreatic cancer trials despite the higher prevalence of these cancers in females.[4] Two studies compared recruitment to cancer clinical trials over time (1990 to 2000 vs 2001 to 2010[33] and 1996 to 2002 vs 2003 to 2016[4]), and both studies found no significant improvement in the representation of women over time.

When examining accrual to trials of breast or gynaecological cancers, studies suggest that older women and minorities are under-represented.[31] Although 42% of all new breast cancers annually are diagnosed in women 65 and older, they represented only 17% of the study participants enrolled onto systemic therapy breast cancer trials through a US cancer consortium (Alliance for Clinical

Trials in Oncology) between 1985 and 2012.[34] In an analysis of 156 NCI-sponsored gynaecological cancer treatment trials, women 65 and older were under-represented in studies of ovarian, uterine and cervical cancer.[35]

Although African-American women have a lower incidence of breast cancer and ovarian cancer compared with non-Hispanic white women, their death rates from breast cancer[36] and ovarian cancer[37] are higher. African-American women are also less likely to enrol in breast cancer[31] and ovarian cancer[35] clinical trials compared with non-Hispanic white women. Distrust in the medical community, which arose in part out of historical research injustices, is a major reason why African-Americans decline to participate in clinical trials.[38] One example is the US Public Health Service Tuskegee Syphilis Experiment[38] which started as a study of the natural history of untreated syphilis in African-American men, but the participants were not given informed consent and did not receive proper treatment for syphilis even after penicillin became available. Another example is the HeLa cell line, which was created from tissue samples obtained in 1951 from Henrietta Lacks, a 30-year-old African-American woman with aggressive cervical cancer.[39] Although the HeLa cell line has been widely used in biomedical research around the world and has led to lucrative discoveries, the Lacks children received no financial benefits and lived in poverty with limited access to healthcare.

Hispanics have a higher risk of infection-related cancers including cervical cancer (typically associated with human papillomavirus, HPV).[40] Indeed, among US Hispanic women, the cervical cancer incidence rate is nearly 40% higher and the death rate is 26% higher than among non-Hispanic white women. In Mexico and Central and South America, the cervical cancer mortality rate is more than three times that of US women, largely due to lack of access to screening and the higher rates of HPV infection. Studies suggest that Hispanic women are under-represented in breast,[4] ovarian and uterine cancer trials but not in cervical cancer trials.[35]

Cancer is the leading cause of death in American Indian and Alaska Native (AIAN) women.[41] AIAN communities represent 1.7% of the US population and are comprised of diverse peoples, with more than 550 federally recognised tribes and villages in the USA. Examination of clinical trials associated with the 31 cancer drugs approved between 2015 and 2018 revealed that 64.5% of the trials did not report any AIAN participants.[42] Across the eight clinical trials involving five drugs FDA approved for breast or ovarian cancer, only 0.5% of the trial participants were Native American.[43]

Those whose genetically assigned sex does not line up with their gender identity may identify as transgender, non-binary or gender-non-conforming. Since gender identity is not routinely collected in clinical trials, surveys or epidemiological studies, very little is known about clinical participation rates of gender minorities.[44] Transgender men and women remain susceptible to cancers of reproductive organs.[45] For example, transgender women who have undergone sex reassignment surgery may still have residual prostate tissue after surgery and thus be at risk for prostate cancer. Little is known about the cancer risk associated with the use of sex hormones used to induce or sustain sex transitions, sometimes in excessive doses or without medical guidance. Discrimination and lack of provider knowledge about transgender health, among other factors, contribute to health disparities in the transgender community. The American Society of Clinical Oncology is working to increase research among sexual and gender minority populations.[44]

While much of the available literature on clinical trial disparities emanates from the USA, it is important to recognise these issues are not unique to the USA. Many of the studies used to support FDA approval are also submitted to other regulatory agencies including the EMA and Health Canada. Non-US participants compromised 69% of the participants in trials leading to FDA approval of novel drugs between 2015 and 2016, and of those non-US participants, 40% were female.[46] The per cent of females among trial participants varied by country (to name a few, 45.2% in Canada, 45.2% in South Africa, 42.1% in Russia, 41.9% in Australia, 40.7% in China, 36.9% in the UK, 29.5% in Norway and 34.3% in India). For oncology drugs receiving FDA approval in 2016, 56% of the participants in trials leading to approval resided outside the USA.

BARRIERS TO ACCRUAL OF WOMEN TO CANCER CLINICAL TRIALS

Many of the barriers to clinical trial enrolment of women are common across all patients including limited awareness of trial opportunities, limited trial availability for the patient's cancer type and stage at the treating institution and overly stringent eligibility criteria.[47 48] Patient-specific factors affecting women include study burden and inconvenience, distrust of researchers and research institutions, lack of understanding about the importance or role of clinical research and fear of risk and randomisation.[49] Negative attitudes towards women as study participants from sponsors and medical professionals may also contribute; these include misperceptions that women are more difficult to recruit,[50] that women are vulnerable to unwilling participation[51] and that women bring complexity to scientific design.[51]

A study of accrual barriers onto breast cancer prevention clinical trials across Massachusetts revealed that a woman is 10.5 times less likely to enrol if she feels that the clinical trial would be too inconvenient.[52] Examples of inconvenience caused by study participation included increased office visits, greater travel requirements, need to maintain daily logs or specific treatment regimens and disruptions on daily lives and family responsibilities.[52] This same study also showed the patient-clinician relationship plays a central role in accrual onto clinical trials, namely that the clinician has sufficient expertise and knowledge and is able to convey the value of the trial to the patient.[52]

Additional barriers exist for minority populations.[30] As previously discussed, lack of trust in the medical community is a major barrier to clinical trial participation in the African-American community, but is also a barrier in other minority groups including AIANs and Hispanics. Many institutions lack outreach programmes in underserved communities. Fewer under-represented minorities receive their care at NCI-designed cancer centres, where many clinical trials in the USA are conducted. Restrictive eligibility requirements, such as cardiac or renal dysfunction, may inadvertently exclude minority populations with a higher prevalence of these comorbidities. For non-English speakers in the USA, language discordance also presents a barrier.[38] Although the US government has a unique trust responsibility to provide healthcare to federally recognised AIAN communities, many barriers exist to cancer care, including historic underfunding of the Indian Health Service, geographical remoteness of many tribal lands, lack of cancer care at local clinics and culturally incongruent care.[53] Poverty is three times higher among AIANs compared with non-Hispanic whites, leading to poorer access to healthcare.[41]

In examining the reasons why elderly women may not participate on breast cancer clinical trials, older patients were less likely to be eligible for available trials and, even when eligible, physicians were less likely to discuss clinical trial participation with older patients.[54] Socioeconomic status may also contribute as elderly women who live in high-poverty areas are less likely to enrol.[55]

ENGAGEMENT, RECRUITMENT AND RETENTION OF WOMEN IN CANCER RESEARCH

Ideally, the population of phase III clinical trials leading to approval of new cancer agents should more closely mirror the population who will ultimately receive these agents. Increasing diversity in trials and studying sex as a biological variable does increase time, effort and costs. Therefore, this effort requires a multifaceted approach with buy-in from patients, medical providers, institutions, trial sponsors, regulatory agencies, among others.

In 2011, the FDA Office of Women's Health, the Society for Women's Health Research and the FDA Office of Minority Health convened the meeting 'Dialogues on Diversifying Clinical Trials' to discuss ways to improve recruitment and retention of women and minorities in clinical trials, among other topics.[50] Recommendations for improving recruitment included diversifying the study team by recruiting female and minority physicians, building trust with patients through communication, education of patients on trial opportunities, education of physicians regarding gender disparities, partnership with women's groups, redesigning clinical trials to improve diversity and incorporation of new technologies for recruitment. More recently, the FDA developed a guidance document on enhancing diversity of clinical trial populations through broadening eligibility criteria and 'improving trial recruitment so that the participants enrolled in trials better reflect the population most likely to use the drug'.[56] Approaches recommended by the FDA include decreasing the burden of trial participation (eg, electronic communications to replace site visits, provide reimbursements for travel and lodging) and adopting enrolment and retention practices that enhance inclusiveness (eg, working directly with patients on clinical trial design, incorporating public outreach and education).

There is also ongoing NCI-sponsored research about how best to diversify clinical cancer trials. EMPaCT (Enhancing Minority Participation in Clinical Trials) is a consortium of five NCI-designated cancer centres with National Institute of Minority Health and Health Disparities research programmes with the aim to increase enrolment racial and ethnic minorities in cancer trials by developing and evaluating recruitment and retention efforts for each major US racial/ethnic category.[57] They have demonstrated that patient navigators and community health advisors (trained lay people who provide culturally appropriate, community based support) help with trial accrual.

Medical societies and journals can also play a role in promoting the study of sex as a variable in oncology clinical trials. The European Society for Medical Oncology (ESMO) convened a multidisciplinary workshop in late 2018 and developed consensus recommendations for studying sex differences in cancer biology and treatment, advocating SABV.[10] The International Committee of Medical Journal Editors (ICMJE) recommends the inclusion of representative populations and the inclusion of sex as a variable.

CONCLUSION

Historically, women have been under-represented in clinical trials. Efforts by various stakeholders including regulatory agencies and women's health advocates have narrowed the gender gap, although women remain under-represented in oncology clinical trials, particularly women from racial/ethnic minority groups and elderly women. Many of the barriers to clinical trial enrolment are not unique to women, although women may face the added misperceptions from some sponsors and medical providers that they are more difficult to recruit and are vulnerable to unwilling participation. Improving recruitment and retention of women and minorities in clinical trials requires a multifaceted approach including education of physicians regarding gender disparities and increased partnership with community members and organisations to help with redesigning clinical trials and patient education.

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