Sex Hormones and Anticancer Immunity

Berna C. Özdemir1,2 and Gian-Paolo Dotto2,3,4

Abstract

The impact of sex hormones on anticancer immunity deserves attention due to the importance of the immune system in cancer therapy and the recognition of sex differences in immunity. Cancer is ultimately the result of failed immune surveillance, and the diverging effects of male and female sex hormones on anticancer immunity could contribute to the higher cancer incidence and poorer outcome in men. Estrogens and androgens affect the number and function of immune cells, an effect that depends on cell type, tumor microenvironment, and age and reproductive status of the individual. Despite the recent progress in immunooncology, our current understanding of the interplay between sex hormones and anticancer immune responses is in its infancy. In this review, we will focus on the impact of sex hormones on anticancer immunity and immunotherapy. We will discuss the potential role of changing hormone levels in anticancer immunity during aging and in the context of menopausal hormone therapies and oral contraception. We will review emerging data on sex differences in PD-L1 expression and potential biomarkers predictive for the efficacy of immune checkpoint inhibitors such as the microbiome and consider ongoing clinical trials evaluating the potential impact of hormone deprivation therapies to increase response to immune checkpoint inhibitors in breast and prostate cancer. Finally, we will point to areas of future research.

Introduction

Sex differences in cancer susceptibility and survival are well documented. Worldwide, men have a higher risk and mortality than women across various cancer types and races, with a few notable exceptions such as thyroid and gallbladder cancer (1). Obvious differences between males and females are sex chromosomes and sex hormones. Both influence self-renewal of target stem cell populations, the tumor microenvironment, and systemic determinants of carcinogenesis, such as cell metabolism and the immune system (2).

A great achievement in oncology in the last years was the recognition of the role of the immune system in cancer development, with the introduction of immunotherapy for a variety of cancer types such as melanoma, lung, and urinary tract cancers (3). It is accepted that cancer development is the result of failed immune surveillance as illustrated by animal models (4) and the increased cancer risk of immunosuppressed patients, as a consequence of organ transplant rejection prevention (5) or HIV infection (6). Tumors showing a strong immune cell infiltration ("inflamed") elicit an innate immune response but escape cell killing by cytotoxic T cells probably through immunosuppressive pathways activated by cancer cells, while in "immune-excluded" tumors, the development of an effective antitumor immune response is blocked by the retention of the immune cells in the tumor stroma. In contrast to the inflamed and immune-excluded tumor types, tumors devoid of T cells ("immune desert") do not activate the innate immune system in the first place (7).

Innate and adaptive immune responses are affected by both chromosomal and hormonal factors and differ between men and women (8). Women have overall stronger immune responses, as shown by the higher incidence of autoimmune diseases in women and data on vaccine and infection responses (8). The sex hormones estrogen, progesterone, and testosterone regulate a variety of cellular functions in both reproductive and nonreproductive tissues, which are yet insufficiently studied (2). Nearly all immune cells express receptors for these hormones (9–13) and many immune-related genes possess androgen receptor (AR)– and estrogen receptor (ER)–responsive elements in their promoters, which may underlie the sex differences in immune responses (14). These can depend on specific immune cell types and their location as well as hormone levels and density and distribution of their receptors. In fact, the same sex hormones can have both immunestimulatory and inhibitory effects as a function of dose(s) and time(s) (15). A comprehensive review of the sex differences in immunity is beyond the scope of this article; for a recent review on the hormonal effects on immune cells, see ref. 8.

Estrogens and androgens have been shown to exert opposite effects on B and T cells, macrophages, neutrophils, and natural killer (NK) cells (10, 16–18). However, it is important to stress that these differences have been mostly studied in mouse models, and whether or not they apply directly to human cells and especially to patients with cancer is currently unknown.

Given that the field is yet developing, the scope of this review is to discuss what we know and what we need to learn about the impact of sex hormones in anticancer immunity in humans in various contexts, such as aging, menopausal hormone therapy, and oral contraception. There is currently considerable interest in cancer immunotherapies and predictive biomarkers of response. We will outline emerging sex differences in efficacy of immune...
checkpoint inhibitors and underlying possible causes, such as levels of PD-L1 expression. Ongoing clinical trials evaluating the potential impact of sex hormone deprivation therapies on response to immune checkpoint inhibitors in breast and prostate cancer will be considered. Finally, we will point to future areas of research such as the impact of pregnancy on anticancer immunity, the role of sex hormones on tumor dormancy, and clinical trial design tailored according to sex hormone levels and other sex differences.

Effect of Sex Hormones on Immunity as a Function of Age

The exponential increase of cancer incidence with age can be attributed to various factors including the accumulation of genetic mutations and changes in the immune system. An essential question to be addressed is how the changes in hormones over the lifespan affect various immune cell types and ultimately the clinical behavior and treatment outcome of various cancers.

Aging exerts a significant impact on estrogen and androgen levels in both males and females with some significant differences and commonalities. While estrogen levels decrease drastically only in women with menopause, there is a rather progressive decrease in androgens in both sexes beginning around the age of thirty (19–21). In turn, the aging process is itself enhanced by decreasing sex hormone levels, resulting for instance in age-related loss of muscle and bone mass and decline of various physiologic functions (22).

Variations in sex hormone levels can now be better appreciated, as a recently developed LC/MS-MS assay allows accurate measurement even of the low levels of testosterone in women (23). Women synthesize androgens and their precursors (e.g., dehydroepiandrosterone, DHEA) in the adrenal glands and ovaries (24) with premenopausal total testosterone levels corresponding to one-twentieth of those found in adult men (20, 25). In men, testosterone is reduced to dihydrotestosterone (DHT), which binds more avidly to the AR. In women, testosterone is present in adipose tissue, skin, bone, and other organs (26). Some studies (27), but not others (28), have suggested that estradiol levels decrease in parallel with testosterone in aging men (Table 1).

In general, considerable interindividual heterogeneity renders the establishment of age-dependent reference ranges for sex hormones in men and women challenging (27). In addition, an individual's true sex hormone status during lifetime is most likely determined by the combination of serum estradiol, testosterone, DHT, and sex hormone binding globulin (SHBG) levels, which determine the concentration of the biologically active free hormone, as well as body mass index (BMI) and sex hormone receptor activity (ref. 29; Table 1).

Aging in men is correlated with a more pronounced decline in total T- and B-cell numbers and a larger increase in senescent CD8 T effector memory cells compared with aging women (30, 31). In women, menopause is associated with an increase in proinflammatory IL-1β, IL-6, and TNFα levels and a reduction in the anti-inflammatory IFNγ levels. Monocytes and NK cells of aged women exhibit a proinflammatory phenotype and more robust cytotoxic activity, respectively, compared with those of aged men. For a recent comprehensive review on the effect of sex hormones on aging and immunity, see ref. 32.

Aging induces a state of chronic low-grade inflammation that has been named as "inflammaging" and which is believed to be the consequence of various inflammatory cytokines secreted by the increasing number of senescent cells in several organs. Multiple stimuli such as oxidative stress, DNA damage, telomere dysfunction, or environmental carcinogens can induce the senescence-associated secretory phenotype (SASP), which has been proposed to be the main origin of "inflammaging" in both aging and age-related diseases such as cancer (33).

Although not reported, it is likely that the physiologic decline in sex hormones during aging plays a role in cellular senescence, which could be of preventive and/or therapeutic significance. In fact, recent evidence from our laboratory indicates that, at least in dermal fibroblasts of both female and male individuals and in fibroblasts associated with skin cancer lesions, genetic or pharmacologic suppression of androgen signaling induces a SASP with associated tumor-enhancing properties, while androgen stimulation exerts opposite beneficial effects. Future work will have to further assess the clinical significance of the findings in the context of other cell types in which androgen signaling may exert a similar or opposite function (34).

Therapeutic Increase of Sex Hormone Levels and Cancer Immunity

The association between cancer risk and changes in sex hormone levels during aging implies that the effect of hormonal therapies on anticancer immunity should be further investigated. In women, menopausal hormone therapies (MHT) using a combination of estrogen and a progestogen (synthetic analogue of

<table>
<thead>
<tr>
<th>Age</th>
<th>Men total testosterone (ng/dL)</th>
<th>Men free testosterone (ng/dL)</th>
<th>Men DHEAS (μg/dL)</th>
<th>Mean estradiol (pg/mL)</th>
<th>Mean free estradiol (pg/mL)</th>
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<tr>
<td>25–54</td>
<td>469–533</td>
<td>9–12</td>
<td>151–286</td>
<td>25.1–25.7</td>
<td>0.54–0.56</td>
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<tr>
<td>&gt;55</td>
<td>469–475</td>
<td>7–8.3</td>
<td>114–137</td>
<td>25.7–29.7</td>
<td>0.46–0.53</td>
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Table 1. Differences in sex hormone levels in men and women during aging

Abbreviation: DHEAS, dehydroepiandrosterone sulfate.
progestrone) are associated with an increased cancer risk of hormone-responsive tissues such as breast (35), endometrium (36), and ovaries (37) to a varying extent, depending on the type of progestogen used (38). This does, however, not occur when estrogen is combined with a natural progestrone (38) and estrogen supplementation alone was reported to decrease (39) rather than increase breast cancer risk. In addition, the response of different tissues and cell types to MHT might also depend on the presence of concomitant risk factors such as obesity and the individual genetic background.

It was reported that MHT partially reverses the impact of aging on immunity by increasing B- and T-cell counts (40), and by decreasing levels of proinflammatory cytokines, TNFα and IL6, in postmenopausal women (41).

Likewise, various forms of hormonal contraception, mostly administered as oral estrogen-progestogen combinations, correlate with a small increase in breast cancer risk (analysis of data from 1.8 million women), which increases with longer durations of use (42). This occurs despite increased numbers of B and T cells (43), suggesting that the direct growth-stimulating effect of sex hormones on the epithelium of reproductive tissues might outweigh effects on the immune system. Experimental evidence for this hypothesis is, however, lacking and differences in types, doses, and duration of hormonal contraception might also alter its impact on immune responses. Long-term oral hormonal contraception is also correlated with increased risk of adenocarcinoma in situ of the cervix (44). While infection with human papillomavirus (HPV) and immunosuppression are established causes of cervical cancer, reports on the association between long-term hormonal contraception use and impaired virus clearance resulting in persistent HPV infections are inconsistent. It is possible that the persistence of only some oncogenic HPV types, such as HPV16, are associated with hormonal contraception exposure (45). Given that most women will be infected with HPV during their lifetime, a possible negative effect of hormonal contraception on immune responses against these viruses needs to be evaluated.

In contrast, hormonal contraception use is associated with a significant reduction of ovarian cancer risk (data from 45 epidemiologic studies; ref. 46) even in BRCA 1 or 2 gene mutation carriers (47). Also, a decreased risk for colorectal and endometrial cancer has been found in hormonal contraception users (48). The mechanisms behind these opposing effects of premenopausal MHT and hormonal contraception on ovarian and endometrial cancer risk are currently unclear and it needs to be determined how the interference with physiologic sex hormone levels and cycles can selectively modulate cancer risk of different organs.

It has not been reported yet whether testosterone replacement therapy influences immune responses in aged men. However, given the growth-stimulating effect of testosterone on prostate tissue, there is the clinical concern that testosterone therapy might increase prostate cancer risk. Although a meta-analysis of clinical trials of testosterone therapy compared with placebo found a nonsignificantly increased rate of prostate cancer and prostate-specific antigen (PSA) levels (49), various other reports indicated that testosterone therapy is safe (50, 51). These seemingly contradictory findings are explained by the “saturation model,” which suggests that the prostate is most sensitive to testosterone effects at very low concentrations when ARs are receptive and becomes insensitive at higher levels. Once the AR is saturated, the presence of additional testosterone appears to have no further effect on prostate tissue (52).

**Sex Differences in PD-L1 Expression and Response to Immune Therapies**

The duration and magnitude of immune responses are tightly controlled by inhibitory immune checkpoints to avoid autoimmunity. These protective signaling pathways are often hijacked by tumors to escape immune surveillance (3). The currently best characterized immune checkpoints are CTLA-4, which is constitutively expressed in regulatory T cells (Tregs) and upregulated upon activation of naïve T cells; programmed cell death protein 1 (PD-1), which is found in T cells, B cells, and NK cells; and the PD-L1, a PD-1 ligand expressed in antigen-presenting cells and cancer cells (53). Some animal studies and emerging clinical evidence suggest a role for estrogens in upregulation of PD-1 and PD-L1 expression (54, 55), and for sex differences in the response to immune checkpoint inhibitors (56–58).

Female sex has been suggested as a negative predictive factor for response of patients with melanoma to anti–PD-1 therapy (56). One explanation for this finding might be the paucity of partially exhausted PD-1high/CTLA-4-positive CD8 cells associated with response to combined checkpoint inhibition in women (59), while a hormone-mediated mechanism might also be important. However, in absence of preplanned subgroup analyses according to sex from large clinical trials or pooled analyses based on individual patient data, no definitive conclusions can be drawn yet.

Robust predictive biomarkers of good therapeutic response, beyond high PD-L1 expression, high tumor mutational burden, or the presence of tumor-infiltrating lymphocytes (TIL; ref. 60), are lacking.

The gut microbiome is emerging as a modulator of response to immune checkpoint inhibitors. In a recent study of patients with melanoma undergoing anti–PD-1 therapy, significant differences were found in the diversity and composition of the gut microbiome of responders compared with nonresponders. Patients with the most diverse microbiome were more likely to respond to immunotherapy, while antibiotic therapy was predictive of resistance to anti–PD-1 blockade. Fecal transplants from responders to germ-free or antibiotics-treated mice resulted in increased antitumor immunity with reduced tumor growth (61, 62).

Studies in mice and human have shown that the gut microbiome is affected by various factors including sex, age, diet, and obesity and itself also contributes substantially to sex differences in immunity (63, 64). For instance, transfer of gut microbiota from adult male mice to immature females changes the recipient’s microbiota composition, leading to elevated testosterone levels and metabolic changes, decreased inflammation, and protection from autoimmune type 1 diabetes (65). Also, gonadectomy and hormone replacement alters microbiota composition significantly in different mouse strains (63). Although the impact of a disturbed relationship between the host and the gut microbiome (dysbiosis) to carcinogenesis in various organs is well established (66), the cross-talk among sex hormones, microbiome composition, and immune system in men and women has as yet to be studied.

Also, obesity was positively correlated with overall survival in men with metastatic melanoma treated with immune checkpoint inhibitors, while no correlation was found in women (67). Although this kind of retrospective analysis has several
limitations, these findings are hypothesis-generating and insinuate possible biological and/or hormonal differences.

A comparison of the PD-1/PD-L1 expression in male versus female patients with cancer of different ages as well as in patients undergoing hormonal therapies is largely missing. Some small studies report an association between elevated PD-L1 expression and male sex (68, 69). Because in current clinical practice, PD-L1 positivity is mostly correlated with poor prognosis, but predictive of response to immune checkpoint inhibitors (60), sex differences in PD-L1 expression could partially account for the overall poorer prognosis of men and better response to immune checkpoint inhibitors. In fact, a recent meta-analysis of clinical trials of immune checkpoint inhibitors for various indications reported a significant survival advantage for men treated with anti–CTLA-4 or anti–PD-1 therapies compared with women (58). Even though these results are not based on individual patient data and the majority of the clinical trials are underpowered to detect clinically relevant sex differences in outcome and rarely report efficacy and toxicity according to sex, these results are thought-provoking. They hint at possible sex differences in the predominant immune escape mechanisms of cancers arising in men and women and indicate that the hormonal milieu might affect therapy response (Fig. 1).

A plethora of checkpoints attenuating (LAG3, TIM3) or stimulating (OX40, CD27) immune responses, respectively, have been identified and are being investigated as potential targets for immune therapies (70). In view of the recent data, the possibility that using different immunotherapy approaches in men and women could improve response rates merits further investigation. In addition, while immunotherapy-induced endocrinopathies are well documented, a possible impact on ovarian and testicular function has not been explored (71).

**Sex Hormone Deprivation Therapies as Coadjuvants for Immune Therapies**

Inhibition of estrogen or androgen signaling is a cornerstone in the treatment of hormone-dependent tumors such as breast and prostate cancers. Although it is difficult to evaluate their effects on antitumor immunity given that these therapies directly act on cancer cells, there is a considerable interest in exploring their impact in cancer immunotherapy in clinical trials (Table 2). It has to be noted that the question whether the immune response itself can be improved by either antiestrogen and antiandrogen therapies alone is not specifically addressed by these trials, and further analysis, for example, on tissue samples from such trials will be required to assess this point and extend similar trial design to other cancer types.

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Sex hormones, genetic factors, and environmental factors contribute to sex differences in anticancer immunity. The cross-talk between sex hormone signaling and genetic and environmental factors affects sex differences in innate and adaptive immunity. Variations of sex hormone levels during aging and pregnancy or due to pharmacologic intervention influence immune responses and can contribute to the sex disparities in oncology, with lower cancer susceptibility in female populations. Emerging data also suggest female sex as a predictor of poor response to immune checkpoint inhibitors. Clinical trials are currently evaluating whether antiestrogen or antiandrogen therapies could improve responses to such therapies. It remains to be determined whether these observed sex differences in immunotherapy responses are possibly due to differences in the predominant immune escape mechanisms in tumors arising in men and women. An effect of sex hormones on disseminated tumor cells and the late relapse of hormone-sensitive malignancies such as breast and prostate cancer as well as on the microbiome needs to be investigated.
Sex Hormones and Anticancer Immunity

Table 2. Clinical trials combining antiestrogen or androgen deprivation therapy with immunotherapies in breast and prostate cancer, respectively

<table>
<thead>
<tr>
<th>Indication</th>
<th>Drugs</th>
<th>Phase</th>
<th>Study ID</th>
<th>Number of participants, primary endpoints</th>
<th>Study completion date</th>
</tr>
</thead>
<tbody>
<tr>
<td>ER+ HER2+ BC</td>
<td>Exemestane + tremelimumab</td>
<td>Phase I</td>
<td>NCT02997995 ULTIMATE</td>
<td>N = 240, pathologic CR</td>
<td>Sep 2020</td>
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<tr>
<td>ER+ BC</td>
<td>Letrozole + pembrolizum + palbociclib</td>
<td>Phase II</td>
<td>NCT02778665 MOPHIEUS</td>
<td>N = 22, ORR</td>
<td>Feb 2019</td>
</tr>
<tr>
<td>HR+ HER2+ BC, premenopausal</td>
<td>Tamoxifen/fulvestran + atezolizumab targeted therapies</td>
<td>Phase I/II</td>
<td>NCT03280563 MOPHIEUS</td>
<td>N = 11, ORR</td>
<td>Oct 2022</td>
</tr>
<tr>
<td>HR+ IBC</td>
<td>Tamoxifen/antagonist inhibitor/LHRH agonist (physician's choice) + pembrolizumab</td>
<td>Phase II</td>
<td>NCT02971748</td>
<td>N = 37, DFS</td>
<td>Jan 2020</td>
</tr>
<tr>
<td>HR+ BC or TNBC</td>
<td>Antiestrogen + pembrolizum + doxorubicin</td>
<td>Phase II</td>
<td>NCT02648477</td>
<td>N = 56, safety, ORR</td>
<td>Sep 2019</td>
</tr>
<tr>
<td>AR+ TNBC</td>
<td>Enzalutamide + enobosam (selective AR modulator) + pembrolizumab</td>
<td>Phase II</td>
<td>NCT02971761</td>
<td>N = 29, safety, ORR</td>
<td>Oct 2019</td>
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<tr>
<td>mCRPC</td>
<td>Enzalutamide + atezolizumab</td>
<td>Phase III</td>
<td>NCT0306312</td>
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<td>mCRPC</td>
<td>Enzalutamide + pembrolizumab</td>
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<td>mCRPC</td>
<td>Enzalutamide + pembrolizumab + enobosam</td>
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<td>NCT02787005 KEYNOTE 199</td>
<td>N = 370, ORR</td>
<td>Mar 2020</td>
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<tr>
<td>mCRPC</td>
<td>Enzalutamide + PROSTVAC-F/V-TRICOM vs. enzalutamide</td>
<td>Phase II</td>
<td>NCT01867333</td>
<td>N = 57, TTP</td>
<td>Jan 2019</td>
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<td>mCRPC</td>
<td>Abiraterone acetate + cyclophosphamide + ipilimumab</td>
<td>Phase I/II</td>
<td>NCT01688492</td>
<td>N = 57, PFS, safety</td>
<td>Sep 2019</td>
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<td>CSPC</td>
<td>Enzalutamide + cycles + pembrolizumab</td>
<td>Phase II</td>
<td>NCT01875250</td>
<td>N = 38, tumor growth</td>
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<td>CSPC, adjuvant or rereurrence</td>
<td>Degarelix (GnRH antagonist) + ipilimumab</td>
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<td>Localized PC, neoadjuvant</td>
<td>Degarelix + cyclophosphamide + QVX vs. degarelix</td>
<td>Phase I/II</td>
<td>NCT01696877</td>
<td>N = 29, CD8+ T-cell infiltration, adverse events</td>
<td>May 2019</td>
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Abbreviations: AR+, androgen receptor positive; BC, breast cancer; CR, complete response; CSPC, castration-sensitive prostate cancer; DFS, disease-free survival; HR+: hormone receptor positive; BC, inflammatory breast cancer; mCRPC, metastatic castration-resistant prostate cancer; NA, not available; ORR, overall response rate; OS, overall survival; PC, prostate cancer; TNBC, triple-negative breast cancer; TTP, time to progression.

Antiestrogen therapies
Tamoxifen and fulvestrant, a selective modulator and degrader of estrogen receptor, respectively, affect antigen presentation. In vitro and mouse experiments have shown a 2–3-fold increased expression of hormonally regulated tumor antigens such as α-Lactalbumin in ER-positive breast cancer cells treated with tamoxifen or fulvestrant (72). This upregulation in expression is correlated with increased anticancer immunity given that tumor-bearing mice respond to treatment with antigen-specific lymphocyte transfer (72). Tamoxifen stimulates neutrophil activity in vitro and in vivo through modulation of sphingolipid biosynthesis (73) and was shown to diminish the number of immunomodulatory myeloid-derived suppressor cells (MDSC) and increase the population of effector and cytotoxic T cells that infiltrated the tumor in a mouse model of ERα-negative ovarian cancer (74).

The aromatase inhibitor letrozole significantly reduces the number of Tregs in human breast cancer tissue, which is correlated with therapy response (75).

These results suggest a potential role for antiestrogen therapies in enhancing the efficacy of immunotherapies and early-phase clinical trials are testing this hypothesis in hormone receptor-positive breast cancers (Table 2).

Androgen deprivation therapies
Similar immune-stimulatory effects were reported with the suppression of androgen signaling (76, 77). Immune cells isolated from men with androgen deficiencies produce more proinflammatory cytokines such as IL1β, IL2, and TNFα when stimulated with lipopolysaccharides (LPS) (78), which is reverts upon testosterone therapy (78–80). Androgen deprivation therapy (ADT), standard of care in prostate cancer, induces expansion of naïve T cells and increases T-cell responses, an effect observed from 1 to 24 months (81). Histologically, ADT is associated with a increase in immune infiltration, adverse events (82, 83). Several studies demonstrated that ADT enhances susceptibility of AR-overexpressing prostate cancer cells to immune-mediated T-cell killing through improved immune recognition (84, 85). Emerging clinical data also reveals that ADT enhances the efficacy of various immunotherapies including immune checkpoint blockade (86) and cancer vaccines such as sipuleucel-T (87) and PROSTVAC (88).

Clinical trials combining ADT with abiraterone acetate, which inhibits androgen synthesis in the adrenals, and enzalutamide, an AR ligand–competitive antagonist with different immunotherapies, are ongoing. These combination therapies might improve the rather poor response rate of patients with prostate cancer to immune checkpoint inhibitors (Table 2).

Animal experiments (89) and data from a phase II clinical trial (88) in prostate cancer suggest that sequential therapy with immune checkpoint inhibitors (Table 2).

Conclusions and Areas of Future Research
Despite the impressive achievements in the field of immunology, our understanding of the interplay between sex hormones and anticancer immunity is lagging behind. The immune
system of females and males evolves in a different hormonal environment resulting in distinct immune responses that vary with the aging-related decline in sex hormones. At the same time, genetic factors such as localization of many immune-related genes and the miRNAs implicated in their control on the X chromosome, are also likely to contribute to the observed sex disparities in immunity (91). In addition to investigating the role of physiologic sex hormone levels and their variation during aging in anticancer immunity, studying the immune system of individuals with pathologic hormone levels or genetic mutations blocking or diminishing male sex differentiation of individuals with XY chromosomes and with or without functioning testicles (e.g., SRY, SOX 9, and AR mutations) could help dissecting the effect of sex hormones from that of sex chromosomes (92, 93).

Furthermore, elucidating the relationship between sex hormones, obesity, the gut microbiome, and immune responses in men and women could improve our understanding of resistance mechanisms to immune checkpoint inhibitors and better select patients who might benefit from these costly therapies.

While immune signals appear to play a role in the reactivation of disseminated tumor cells (DTCs) surviving in a "dormant" state in distant organs, the influence of sex hormones in this context is, however, currently unknown (94). Because hormone-responsive tumors such as ER-positive breast cancer and prostate cancer can relapse after years or even decades of apparent remission, investigation of a possible association between changes of sex hormone levels during aging or pharmacologic treatment and reawakening of DTCs is of great clinical interest (Fig. 1).

Various topics such as the impact of pregnancy on cancer relapse are still a matter of debate with controversial findings (95). There is an unmet need to thoroughly characterize the immunologic changes that occur during pregnancy and systematically collect data on pregnancy-associated cancers. Evidence-based recommendations regarding pregnancy are required to appropriately counsel the increasing population of cancer survivors in child-bearing age.

Finally, we need to revisit clinical trial design in immunotherapy. The trend is empirically combine different immunotherapy approaches with or without standard therapies is increasingly questionable. This approach should be replaced by rational combination strategies based on a better understanding of the mechanism of action and the effects of sex hormones and hormones on immune responses. Also, the reporting of trial results should contain subgroup analyses according to sex and discuss whether the study was sufficiently powered to detect potentially relevant sex differences, the plausibility of the findings, as well as their biological basis. A close collaboration between different institutions and data sharing could help advance the field of immunono-cology.

Disclosure of Potential Conflicts of Interest
No potential conflicts of interest were disclosed.

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References

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44. Polanczyk MJ, Hopke C, Vandenberg AA, Offner H. Estrogen-mediated immunomodulation involves reduced activation of effector T cells, poten-


