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Review Article

Renal Dysfunction in Gynaecological Cancers

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Abstract

Gynaecological malignancies (cancers of female reproductive organs) account for one of out of six cancers in women worldwide. Although there are many risk factors associated with the incidence of such malignancies, such as parity, obesity, the use of birth control pills or oestrogen therapy, hysterectomy, endometriosis, and the woman's lifestyle, it is not often appreciated that cancer incidence may also be associated with renal dysfunction. Lower estimated glomerular filtration rates (eGFR) are involved in gynaecological malignancy development, especially in those of the ovary, cervix, and endometrium. Recent evidence also indicates an association between reduced renal function and other cancers including those of the female breast and vagina. In this review, we re-examine the available evidence for a bi-directional link between the dysfunctional kidney and gynaecological cancer incidence and development. Although the data are scarce, interest in this area is increasing and has indicated that the new sub-specialty of onconephrology may help answer the question of whether the dysfunctional kidney is a causative agent in the development of the cancer, or if the cancer is the cause of the loss of eGFR. The role of misleading markers of gynaecological cancers is demonstrated along with how onconephrology might aid the busy gynaecology oncologist in the treatment of their patients, by highlighting which chemotherapy should be used and what effect reduced dosing might have. This controversy is discussed. The paucity of studies in this area suggests studying the associations between reduced renal function and gynaecological cancers would be beneficial, not only to the patient but also to the gynaecology oncologist.

Keywords: eGFR; Chronic Kidney Disease (CKD); Renal Function; Reduced Renal Function; Endometrial Cancer; Gynaecological Cancers; Ovarian Cancer; Cervical Cancer; Breast Cancer.

Introduction

The interplay between different organs of the body often indicates the normal physiology of the organs involved. For example, a fully functional hypothalamic-pituitary-gonadal axis is critical for the normal function of the reproductive organs [1]. What is not often appreciated is that other organs in the body, when dysfunctional, may impact directly or indirectly on a body system's normal physiology, or that dysfunction in a distal organ may be a marker of disease within the pertinent body system. In this review, the impact of renal impairment and dysfunction will be examined in relation to gynaecological cancers, and vice versa.

Methods

To identify suitable original research articles, review articles and clinically relevant websites, the Medline (1966-date), Scopus (2004-date), Clinicaltrials.gov (2008-date), EMBASE (1980-date), and Google scholar (2004-date) databases were scanned in a primary search along with the reference lists of electronically retrieved full-text papers that were identified. The date of our last search occurred on September 28th, 2023. Our search strategy included the text words hydronephrosis; ureteral dilatation; acute kidney damage; chronic kidney damage; renal failure, or glomerular filtration rate and these were combined with gynaecological cancer; endometrial cancer/carcinoma; ovarian cancer/carcinoma; breast cancer/carcinoma; cervical cancer/carcinoma; vaginal cancer/carcinoma; vulval cancer/carcinoma or oviductal/Fallopian tube cancer/carcinoma. Suitable publications or websites were selected in consecutive stages.

Following deduplication, the titles, abstracts, and reference lists of all articles were screened by the authors to assess their eligibility. The decision for inclusion of studies in the present review was taken after retrieving and reviewing the full text of articles that were considered as potentially eligible. Conference abstracts were also considered as eligible and included where appropriate. Manuscripts not published in English were translated using Google Translate. Experimental animal studies were not included in the present review.

Gynaecological Cancers

Gynaecological cancers initiate and are generally localised to the female reproductive organs (**Figure 1**), with endometrial cancer, ovarian cancer and cervical cancer being the most common [2-5]. Some oncologists also include neoplasms of the breast as being gynaecological in nature and so these are also included in this review [6-9]. In this regard, breast cancer is the most common of all 'gynaecological' cancers in the USA, China, the United Kingdom, and the remaining members of the European Union (**Table 1**;[2-5,10]). Less common gynaecological cancers such as those of the vulva, Fallopian tube (oviductal), uterine wall (sarcoma), vagina, and those found in pregnancy such as choriocarcinoma and molar pregnancy, are much rarer or often not recorded in cancer statistic tables (**Table 1**; [3,510,11]). Although the incidence and death trends for breast cancer and cervical cancer in some regions of the world are in decline, other cancers such as ovarian and endometrial cancer are showing increased incidence and mortality rates [3,10,11]. Some commentators on this phenomenon cite the recent lack of access to healthcare due to the COVID-19 pandemic as a contributory factor to the estimated increases in gynaecological cancer incidence and mortality, especially in the USA [5,12,13]. Similar trends have been reported in the United Kingdom and Europe [2,11].

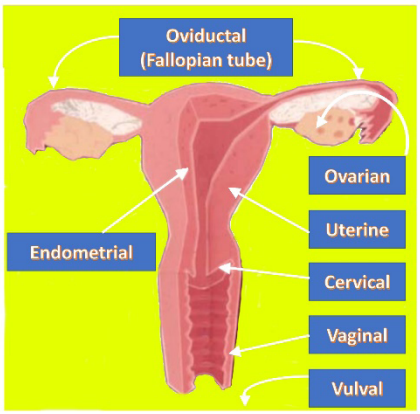

Figure 1: Sites of gynaecological cancers in the female reproductive tract; The most common sites for gynaecological malignancies are depicted. The vulva is outside of the image as is the breast. Uterine cancers other than those of the endometrium and those of pregnancy are not included in this review and so are not included in the figure.

	USA[1]		**China[1]**		**Europe[2]**		**UK[3]**	
Cancer type	Estimated new cases	Estimated deaths	Estimated new cases	Estimated deaths	Estimated new cases	Estimated deaths	Estimated new cases	Estimated deaths
Breast	259827 to 287850	43250 to 44094	429105	124002	531086	141765	55920	11499
Endometrial	63246 to 69950	11909 to 12550	84520	17543	130051	29963	9703	2453
Cervical	13740 to 14100	4280 to 5830	111820	61579	58169	25989	3197	853
Ovarian	19880 to 24494	12810 to 14914	57090	39306	66693	44053	7495	4142
Vulval	6317 to 6330	1551 to 1560	3516	1319	16506	6503	1372	469
Vaginal and other reproductive tissues	1496 to 8870	431 to 1630	1711	720	2947	1267	250	110

Table 1: Estimated incidences and mortality figures for gynaecological cancers in the USA, China, Europe, and the UK, 2020-2022; [1] Estimates based on data released by the international agency for research on cancer for GLOBOCAN 2020 and the WHO for World Population Prospects (2019 revision) [3] and [2] Cancer Statistics in China and United States, 2022 [5]. [3] (ECIS - European Cancer Information System, 2023 [4]).

After breast cancer, endometrial cancer is the most common cancer in adult female reproductive organs with more than 417,000 women diagnosed worldwide in 2020 (https://www.wcrf.org/cancer-trends/endometrial-cancer-statistics/. It is estimated that one out of every 40 women are destined to develop this type of neoplasm by the end of this decade [14]. Most (80-90%) endometrial cancers are of the endometroid type and are caused by exposure to endogenous or exogenous oestrogens, either through ovarian secretion or as part of a post-menopausal hormone replacement therapy [15]. Treatment of women with tamoxifen or other SERMs as part of their therapy for breast cancer or to reduce the risk of osteoporosis may also increase the risk of endometrioid endometrial cancer [16]. The most common cause of the excess oestrogen production in pre- and post-menopausal women comes from being overweight since adipocytes also have the ability to synthesise a number of natural oestrogens [17]. A smaller number of endometrial cancers (10-20%) are not dependent on oestrogenic stimulation and have a series of molecular alterations that result in uncontrollable cellular proliferation [18]. These are designated non-endometrioid endometrial cancer and appear to have a worse prognosis than their endometrioid counterpart [19].

The next most prevalent gynaecological cancer behind breast and endometrial cancer is ovarian cancer, which is often not detected until it has already metastasised to other parts of the body [20] and so becomes incurable [21]. More women die from ovarian cancer than all other forms of gynaecological cancer combined [2-5]. The molecular mechanisms that result in the development of ovarian cancer are currently incompletely understood, although oestrogen excess is again a known risk factor [22]. A key area of intense research is the discovery of biomarkers for early ovarian cancer discovery and patient prognosis [23-25]. Of these, the expression of human epididymis 4 protein (HE4) is considered a key serum protein biomarker for early ovarian malignancy [26-29]. It is also suggested that this protein may be a good marker for breast [30], endometrial [31], lung [32], pancreatic [33], gastric [34] and cervical cancer [35]. It is currently unknown if this protein is a marker for cancers other than those listed above [36].

Cervical cancer was once the most common gynaecological cancer worldwide and is thought to be caused by exposure to different strains of the human papilloma virus (HPV), which is a sexually transmitted disease that also causes anogenital warts [37]. Cigarette smoking is also strongly associated with the development of cervical cancer, whilst the use of the Pap test (in the UK, cervical smear in other parts of the world) has greatly reduced cervical cancer prevalence and mortality by allowing early detection and treatment of tissue abnormalities before the cancer becomes a series health concern [37].

While significant progress has been made in reducing the incidence of some gynaecological cancers, the same cannot be said of other female genital tract cancers. This may partly be due to the lack of a thorough understanding of their pathogenesis. For example, the most up-to-date information on vulval cancer suggests it is the next most common female reproductive tract cancer in all regions of the world, with European women particularly susceptible to the development of this neoplasm (**Table 1**). The molecular and cellular causes of vulval cancer are relatively poorly understood, even though lichen sclerosis/planus and vulval intraepithelial neoplasia appear to be key risk factors [38] especially in women who are HIV positive [39]. The precise molecular mechanism(s) that result in this disease remains obscure, although HPV infection is again implicated [37], since women with cervical cancer are also prone to concurrent vulval cancer development [40].

The least common cancer of the female reproductive tract is found in the vagina (**Table 1)**. The actual numbers of women with vaginal cancer is difficult to estimate because incidence of this cancer is often included in a subsection of cancers that include oviductal and placental aberrations [4]. Nevertheless, all these various gynaecological cancers create a large healthcare burden worldwide, that currently seems to be intractable.

Recent reports suggest that many of these gynaecological cancers are closely associated with kidney disease or renal dysfunction [41-45]. Others dispute this claim [46]. In this review, we re-examine the available evidence to reach a consensus on whether an association between each gynaecological cancer and renal dysfunction exists, or not. Important discoveries on HE4 expression in renal dysfunction will also be discussed.

Determination of Renal Dysfunction

Impaired renal function has been reported as an independent risk factor for morbidity and mortality in the general population [47]. In this regard, three conditions should be considered: (1) acute kidney injury (AKI), (2) chronic kidney damage (CKD), and (3) total renal failure [48]. To define each of these, some strict clinical parameters need to be determined. In the case of AKI, this can be divided into pre-renal (e.g. hypovolaemia, decreased cardiac output), intrinsic renal (e.g. use of nephrotoxic drugs, interstitial nephritis), and post-renal (e.g. renal stones, ureteral calculi, bladder outflow obstruction from prostate enlargement). According to NICE guidelines in the UK (https://cks.nice.org.uk/topics/acute-kidney-injury/), diagnostically AKI can be detected by using any of the following criteria [49]:

- A rise in serum creatinine of 26 μM or greater within 48 hours
- A 50% or greater rise in serum creatinine known or presumed to have occurred within the past 7 days, or
- A fall in urine output to less than 0.5 mL/kg/hour for more than 6 hours.

The problem with these definitions is that a starting serum creatinine level needs to be determined prior to diagnosis. Nevertheless, AKI is often reversible if the causative insult is removed [50]. If not, then AKI can develop into chronic kidney disease (CKD) [51], which according to NICE guidelines in the UK (https://www.nice.org.uk/guidance/qs5) is defined by the following criteria:

- decreased kidney function shown by an estimated glomerular filtration rate (eGFR) of less than 60 mL/min per 1·73 m^2, or
- the presence of markers of kidney damage of at least 3 months duration, regardless of the underlying cause.

CKD is often treatable, but not curative [52]. Total kidney failure (requiring dialysis or organ replacement) occurs when all kidney function ceases [53] or when urine output is less than 15 ml/min. This is classified as CKD stage 5 and is irreversible [53] and is also called end-stage kidney disease (ESKD) or end-stage renal disease (ESRD).

As can be seen above, there are two key clinical measurements that can be used to determine the level of tissue damage that indicates renal dysfunction: (1) creatine clearance rates and (2) estimated glomerular filtration rates (eGFR). These two parameters are intimately linked, with eGFR being the current measurement of choice [54].

a. Creatinine and its renal clearance

Creatinine is a by-product of ATP synthesis and muscle protein activity or metabolism, the ingestion of cooked red meat and the breakdown of muscle during strenuous exercise [55]. It is released into the circulation at a constant rate and almost exclusively eliminated from the body by the kidney [56]. As such, it is a good indicator of normal renal function [56]. Renal dysfunction can be determined by measuring serum creatinine levels using the following criteria:

- A rise in serum creatinine of 26 µM or greater within 48 hours (may be indicative of kidney dysfunction). It is, however, important to realise that in the absence of a baseline creatinine value, a high serum creatinine level may indicate AKI, even if the rise in creatinine over 48 hours is less than 26 µM (particularly if the person has been unwell for a few days).
- A 50% or greater rise in serum creatinine (more than 1.5 times baseline) known or presumed to have occurred within the past 7 days.
- A fall in urine output to less than 0.5 mL/kg/hour for more than 6 hours (if it is possible to measure this, for example, if the person has a urinary catheter).

An alternative method is to collect urine over a 24- or 48-hour period and measure the concentration of creatinine in the urine over that period [57].

The rate of creatinine clearance in most normal adult women is somewhere between 88 and 128 ml/min, but that rate can be affected by several factors including age, ethnicity, levels of hydration, protein intake or muscle usage/damage [56]. As women age, their creatinine clearance rates decline and serum creatinine levels increase [58]. Creatinine is removed from the blood chiefly by the kidneys, primarily by glomerular filtration in the Bowman's capsule, but also by proximal tubular secretion; little or no distal tubular reabsorption of creatinine occurs (**Figure 2**) [59].

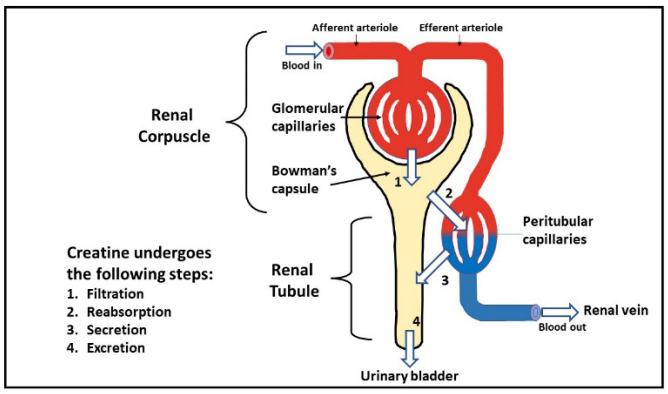

Figure 2: Sites and general mechanisms of creatinine transport in the kidney nephron; (Step 1.) Initially creatinine is filtered from afferent capillaries across the squamous epithelia of the Bowman's capsule. Specific membrane transporters in the proximal collecting duct tubules and peritubular endothelium reabsorb some of the creatine. (Step 2.) As creatinine travels through the peritubular capillaries, changes in blood pH induce (Step 3.) secretion of creatinine back into the glomerular filtrate, which then (Step 4.) travels out of the kidney cortex into the renal pelvis on its journey to the urinary bladder.

b Glomerular Filtration Rate

If filtration in the kidney is deficient, serum creatinine concentrations rise. Therefore, creatinine concentrations in blood and urine may be used to calculate the creatinine clearance rates given above, which correlates approximately with the glomerular filtration rate (GFR) according to the equation:

$$GFR = \frac{Urine\ concentration\ x\ Urine\ Flow}{Serum\ concentration}$$

The normal range of GFR, adjusted for body surface area, is 90-120 mL/min/1.73 m^2 in women younger than 40 years of age. After 40 years of age, GFR decreases progressively by 0.4-1.2 mL/min per year Koperska, M. and Michałowska, J. Creatinine Clearance calculator (https://www.omnicalculator.com/health/crcl). GFR when adjusted for body surface area is a definition of estimated GFR (eGFR) and this is now recommended in clinical

practice guidelines and by regulatory agencies for routine evaluation of GFR [60]. By contrast, measured GFR is recommended as a confirmatory test when more accurate assessment is required [60]. In this case, serum creatinine concentrations alone may also be used to estimate GFR (eGFR) and this is the primary modern method for determining renal function in most countries [61-63].

Estimated Glomerular Filtration Rate (eGFR)

Glomerular filtration rate (GFR) represents the flow of plasma from the glomerulus into Bowman's space over a specified period and is the chief measure of kidney function [54]. The kidneys receive 20% to 25% of a person's cardiac output (about 1.0 to 1.1 litres per minute) with the blood entering individual glomerular tufts *via* an afferent arteriole and exiting through an efferent arteriole (**Figure 2**; [64]. The glomerular filtration rate (GFR) is equal to the sum of the filtration rates in all the functioning nephrons; thus, the GFR gives an approximate measure of the number of functioning nephrons within the kidneys. The normal value for GFR depends upon age, sex, and body size, and is approximately 90 to 120 mL/min/ for younger women, with considerable variation even among normal individuals [65]. GFR can be measured using 4 main methods. As described above, the most widely used measurement is that based on the Cockcroft and Gault equation that estimates GFR over a 24-hour period [66]. This equation considers a patient's age, body mass and gender, with serum creatinine measured in mg/dL. The equation:

$$eCcr = \frac{(140 - Age)x\ Mass\ (in\ kiograms)x\ [0.85\ if\ Female]}{72\ x\ [Serum\ Creatinine\ \left(in\ \frac{mg}{dL}\right)]}$$

was first presented in 1976 and is popular because it can be determined with a desktop calculator but does not consider the ethnicity of the patient, a strong criticism of this method. To account for this factor, the Modification of Diet in Renal Disease (MDRD) formula has been used in UK laboratories, but that too has been criticised because this formula does not adjust for the patient's body size [67]. To counter all of these issues, the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula was created in 2009 and subsequently adopted by NICE in the UK (https://www.nice.org.uk/guidance/cg182 - investigations-for-chronic-kidney-disease-2). The CKD-EPI equation is:

$$eGFR = 141 \times \min(SCr/k,1)^{a} \times \max(SCr/k,1)^{-1.209} \times 0.993^{Age} \times [1.018\ if\ Female] \times [\ 1.159\ if\ Black]$$

where SCr is serum creatinine (mg/dL), k is 0.7 for females and 0.9 for males, a is -0.241 for females and -0.302 for males, min indicates the minimum of SCr/k or 1, and max indicates the maximum of SCr/k or 1, and Age is in years. Despite its overall superiority to the MDRD equation, the CKD-EPI equations performed poorly in certain populations, including black women, the elderly and the obese, and is less popular among clinicians than the MDRD estimate [68]. Nevertheless, it remains useful in a clinical setting, especially when accurate estimates are required for patients with cardiovascular risk [62].

Because of the non-standardisation problems of the different eGFR methods available based on serum creatinine measurement, a gold-standard method was sought. Injection of inulin or the inulin-analogue sinistrin (a mixture of natural polysaccharides) into the circulation is now the definitive method of choice because both inulin and sinistrin are neither reabsorbed nor secreted by the kidney after glomerular filtration (**Figure 2**), and so their excretion rate is directly proportional to the rate of glomerular filtration. Nevertheless, this method has one serious drawback in that incomplete urine collection, or not including muscle mass into the formula, creates an underestimate of the eGFR [69]. Using inulin to measure kidney function is presently considered the "gold standard" when compared with other means of eGFR and has been for some time [63].

GFR can also be accurately measured using radioactive substances. In this situation, patients are injected with trace amounts of either chromium-51 (the actual gold standard measure in UK guidance (https://www.nice.org.uk/guidance/cg182#when-highly-accurate-measures-of-gfr-are-required) or technetium-99m, because ^{51}Cr-EDTA (the material used in Europe) is not available in the USA [70]. These materials come close to the ideal properties of inulin (undergoing only glomerular filtration) but can be measured more practically with only a few urine or blood samples [71].

Problems with the measurement of serum or urinary creatinine (varying muscle mass, recent meat ingestion, strenuous exercise, etc.) led the use of serum cystatin C for GFR measurement. Cystatin C is a ubiquitous enzymatic protein secreted by most cells in the body that is freely filtered at the glomerulus and then reabsorbed and catabolised by the tubular epithelial cells, with only small amounts excreted in the urine. Cystatin C levels are therefore measured not in the urine, but in blood. Equations have been developed linking estimated GFR (adjusted for sex, age, and race) to serum cystatin C levels (also adjusted for sex, age, and race) and combined with creatine measurement after adjustment for sex, age, and race [61]. It therefore appears that use of adjusted eGFR and adjusted serum cystatin C levels provide the best estimates of kidney function or dysfunction.

All the different methods to measure GFR and eGFR have their problems, but inulin is the only method that has no bias and thus remains the gold-standard [63].

Clinical significance of eGFR

Changes in GFR and eGFR are used to define and diagnose several pathologies in the general population. Acute kidney injury

(AKI) is an abrupt increase in serum creatinine (generally over days) and the reduced GFR is largely reversible. Alternatively, chronic kidney disease (CKD) is often irreversible, and persists for at least 3 months [65]. CKD is staged as follows:

- Stage 1 normal, glomerular filtration greater than 90 ml per minute
- Stage 2 mild, 60 to 89 ml per minute
- Stage 3a mild to moderate, 45 to 59 ml per minute
- Stage 3b moderate to severe, 30 to 44 ml per minute
- Stage 4 severe, 15 to 29 ml per minute
- Stage 5 failure, less than 15 ml per minute

These CKD stages are often related to cancer progression and can possibly be used to inform treatment choices for patients with all forms of gynaecological cancer (see final section).

eGFR and Cancer of any type

Patients with mild or moderate chronic kidney disease (CKD) have an increased incidence for many different types of cancer [72,73]. The threshold of CKD associated with cancer incidence remains undetermined, but a decrease in eGFR is associated with increased cancer risk [74-81], with higher rates reported for some cancers in men [82]. Although the pathophysiologic mechanism(s) for this increased incidence is not explained, or at least is not fully understood, eGFR decline is associated with high grade tumour activity [82]. Patients with a GFR below 60 ml/min have an increased cancer-related mortality [72,82], with the suggestion that acceleration of cell differentiation is caused through the presence of uremic toxins, while chronic inflammation and oxidative stress leads to cancer cell proliferation and tumour angiogenesis [83]. The available data suggests that the uremic milieu produces more aggressive cancers with higher histology grades [83]. This in turn causes an impairment of various immune cells and their antitumor activity that results in bigger and more rapid cancer growth [83]. One interesting observation is that anaemia, as a common CKD manifestation, is often associated with poorer survival of patients with all forms of cancer [84]. The exact mechanism(s) involved is uncertain, but what is clear is that in the presence of either microcytic or macrocytic anaemia, cancer sample size, cancer stage, and histology grade are all increased [85].

Although there are various risk factors associated with female genital cancer incidence, such as parity, use of oral contraceptives, post-menopausal oestrogen replacement therapy, hysterectomy, endometriosis, and obesity [86], there are conflicting reports on increased risk of female reproductive tract cancers that have an association CKD. What is clear is that renal dysfunction has serious implications for treatment and prognosis of patients with these gynaecological cancers.

eGFR and Gynaecological Cancers

Gynaecological cancers share a unique anatomical relationship with the female urinary tract with implications for direct and lymphatic spread in advanced and metastatic disease [87]. In patients with kidney disease, a reduction in eGFR implies either progression of the underlying disease or the development of a superimposed and often reversible problem. Many studies suggest that cancer risk is increased in CKD patients. In 1999, Maisonneuve and co-workers assembled a cohort of 831,804 patients, including men and women who received dialysis in the USA, Europe, Australia, and New Zealand. These authors found a significant 18% higher risk of cancer in patients with CKD [relative risk (RR) 1.18, 95% CI 1.17-1.20] [88]. The authors found that the excess of cancer varied in the different regions, ranging from the highest relative risk (RR) of 1.8 (95% CI 1.7-2.0) in Australia and New Zealand to the lowest RR of 1.1 (95% CI 1.0-1.1) in Europe.

They also found increased cancer risks were seen in younger patients (RR 3.68, 95% CI 3.39-3.99), and for several sites of cancer, including the well-known kidney and urinary bladder, and lower genital tract in women [87]. These authors speculated that the excess cancers in the CKD patients could be explained in several ways. For example, the presence of chronic infection, especially in the urinary tract; a weakened immune system; previous treatment with immunosuppressive or cytotoxic drugs [64]; nutritional deficiencies; altered DNA repair; and the presence of an underlying disease or co-morbidity, such as diabetes mellitus, acquired renal cystic disease, or obesity, which might predispose to the patient to cancer initiation or development. What they did not do, was look at the relationships between markers of kidney function and the individual gynaecological cancers.

On the other hand, there have been contradictory findings. A cohort study using a total of 3045 women with a diagnosis of CKD was conducted by Chang and co-workers in 2018. In their study they investigated the risk of female genital tract related cancer (gynaecological cancer: GC) or breast cancer (BC) of women with CKD with the suggestion that the risks might be different from that of those women without CKD [46]. The study indicated that the women with CKD had a lower risk of female genital tract related cancer (GC) than the non-CKD affected women (crude hazards ratio (HR) 0.57, 95% CI 0.39-0.81). Similar data was found in the patients with BC. To further clarify which of the various gynaecological cancers contributed to this reduced effect of CKD, they compared the rates of each cancer between women with and without CKD and found that cervical cancer (1.05% *vs* 1.54%), uterine cancer (0.33 *vs* 0.89%), epithelial ovarian cancer/ tubal

cancer (0.13% *vs* 0.39) all occurred at the lower rate in the CKD affected women. These data suggested that CKD was protective against the development of these forms of gynaecological cancer and contradicts previous work [87]. Subsequent studies however support the work of Maisonneuve et al. [89], suggesting a cohort effect may be the cause of the discrepancies between these three studies.

eGFR and Endometrial Cancer

The number of studies examining the relationship between kidney damage and the two forms of endometrial cancer are few [89-93]. The available evidence suggests that patients with lower eGFR levels have an increased risk for higher histological grades and stages of these cancers [89]. For example, Premuzic and colleagues [89], divided their patients into two subgroups based on a GFR cut-off point of 60 ml/min, and demonstrated that a GFR lower than 60 ml/min was significantly related to higher cancer grades (II-III; odds ratio 1.06; 95% CI 1.02-1.11) and cancer stages 2-4 (odds ratio 1.06 95% CI 1.01-1.09). Their conclusion was lower GFR was a stronger independent predictor of higher endometrial cancer histology grade and higher cancer stage than more traditional predictors, such as age, diabetes, the menopause, or obesity [89]. A significant component of the cause in this patient cohort was attributed to the inability of the patients to eliminate oestrogen from the body [87,94], resulting in endometrioid cancer development and progression [95].

An interesting additional observation is that components of the renin-angiotensin-aldosterone system are present in the normal endometrium but elevated in the endometrium of patients with endometrial cancer [96,97]. The renin-angiotensin-aldosterone system is a key regulator of renal function and so changes in the endometrium during endometrial cancer development could dysregulate the nephron *via* this route. This is not a new observation, since renin has previously been demonstrated to be present in the decidua, and in other forms of cancer [98-100]. The implications of these observations are that the kidney, and its normal function, is intimately associated with the endometrium and its normal function. A consequence of dysfunction in either of these organs may therefore precipitate dysfunction in the alternate organ [45,101,93,102]. The potential interaction between novel, previously unidentified proteins unique to endometrial cancer and kidney dysfunction remains to be elucidated [103].

eGFR and Ovarian Cancer

Few data are available regarding renal impairment in ovarian cancer patients. There is some evidence to suggest reduced renal function is also associated with elevated levels of CA125, a marker of ovarian cancer [104] and inflammatory biomarkers, particularly C reactive protein, but not eGFR in ovarian cancer risk [105]. A study by Donadio and colleagues [106], investigating the prevalence of renal functional impairment and morphological alterations in patients with ovarian cancer at the time of diagnosis, found a 28% reduction in renal function and a moderate to severe dilation of the upper urinary tract occurred in 18% of the ovarian cancer patients at the time of the diagnosis. These patients were all asymptomatic with respect to their kidney dysfunction, meaning that their impaired renal status would be undiagnosed. This could be potentially damaging to the patient since assessment of renal function in ovarian cancer patients (as it is for all other cancer patients) is important when calculating the dose of carboplatin (or the more toxic *cis*-platinum-based chemotherapy) to be administered to ovarian cancer patients [107]. Based on the findings of Donadio and colleagues, an early referral of ovarian cancer patients (and possibly all gynaecology cancer patients) to a nephrologist or onconephrologist is recommended [106], especially if platinum-based chemotherapy is being considered. A surprising finding from this one study was that plasma creatinine levels were normal in patients when the eGFR was less than 40 ml/min/1.73 m^2, leading to the speculation that this unexpected observation was due to a lower muscle mass in these patients due to their advanced age. More importantly, this speculation could be incorrect, but instead be caused by inappropriate methodology [108]. In addition, the introduction of pegylated liposomal doxorubicin, gemcitabine, topotecan, or bevacizumab to existing platinum- or taxane-based chemotherapy regimens may exacerbate existing nephrotoxicity issues [108].

This idea is complemented with the observations of Fan and co-workers [109] who demonstrated that the often cited early diagnostic marker of ovarian cancer HE4 is not a good indicator of disease because it provides a false-positive signal, especially in patients with CKD [110,111], or when co-morbidities, such as breast [112] or lung [113] cancer, or in patients with heart failure [110], are present. The use of Poly (ADP-ribose) polymerase inhibitors has been encouraging, even though there is an initial reduction in eGFR [114], it rebounds by 12 months to levels similar to ovarian cancer patients receiving carboplatin and paclitaxel. These data suggest that more targeted or cancer-specific biomarkers are needed when diagnosing, treating or monitoring the different gynaecological cancers before and after treatment [103,115].

eGFR and Cervical Cancer

Patients with CKD are often stated to have an immunosuppressive status [64]. Such women might therefore have an impaired ability to eradicate any incipient pathogen, i.e., those with cervical or vulval/vaginal cancer, who may not be able to eradicate their human papilloma virus (HPV) infection, [64]. Additionally, it has been suggested that these women with CKD have a limited immune response to HPV infection that subsequently develops into a prolonged latency or persistence of

the HPV infection, that results in the development of pre-cancerous lesions that ultimately become malignant [116]. Furthermore, some studies demonstrated that women with CKD were substantially less likely to undergo cervical cancer screening compared to women without CKD [89,117], explaining or at least supporting a reason for the finding of a 2.5-fold increased risk of cervical cancer in women with CKD that has an autoimmune component [118]. Hydronephrosis (swollen kidney) is also associated with cervical cancer development [42,44,119,120] and seems to occur because of the cervical cancer rather than being the cause of the cervical cancer [44]. How this comes about can only be speculated upon. Uretic stenting or urine diversion can provide symptomatic relief for such patients but does not significantly affect outcomes, even if the hydronephrosis was discovered before the cervical cancer [120], although the patients age, the presence of type 2 diabetes mellitus and the stage of hydronephrosis are strong predictors of a worsening survival rate in patients with advanced cervical cancer [121].

eGFR and Breast Cancer

Although breast cancer is the most common cancer affecting women, the data available on the relationship between eGFR and breast cancer is scarce [8,43,46,116,122-124]. The available data are controversial with studies indicating that CKD and thus lower eGFR is not a risk factor for breast cancer patient development or survival [43,46]. The issue with these small studies is that treatment of breast cancer patients with conventional radio- or chemotherapy is contra-indicated in patients with renal insufficiency, but not those on dialysis [125] as it is for patients with gynaecological cancers [126-129]. A recent study has also proposed HE4 as an independent biomarker for breast cancer [30] despite this protein being used in ovarian cancer diagnosis [28,29,130], ovarian cancer prognosis after treatment [130], and also being identified in the low eGFR state of CKD or nephritis [131,132]. HE4 production occurs even in women with normal ovarian function [133], all despite its expression patterns in multiple tissues and organs being known for many years [134]. Additionally, elevated HE4 levels are found in non-malignant gynaecological conditions [111], suggesting that HE4 expression could reflect kidney dysfunction rather than the incidence and progression of neoplasia in the genital organs [135-137]. Indeed, we have previously demonstrated that transcripts for the HE4 protein are not even generated in endometrium epithelial cells in response to exogenous oestradiol and tamoxifen (as might be expected in endometrioid endometrial cancer), but is repressed in the endometrial stromal cell in response to these ligands [138]. Furthermore, the idea that pelvic masses might be benign whilst CKD is present was reported for an Italian woman in preparation for kidney transplant [139]. These data suggest that HE4 is probably not a good diagnostic or prognostic marker for women with gynaecological cancers who also have renal dysfunction. Of course, more definitive research in this area is required.

eGFR and Vaginal, Vulval and Oviductal Cancers

Cancers of the vagina, vulva and oviduct are rarely observed [2-5] and less studied when compared to other gynaecological cancers. This is despite a significant number of women worldwide estimated to die with these forms of gynaecological cancer (**Table 1**; [2-5,9]). Accordingly, only scant literature exists on the effect of renal dysfunction on the incidence and mortality levels that can be attributed to reduced eGFR is these patients, and the only study available appears to be associated with HPV infection and immunosuppression in renal transplant patients [140]. The treatment of vulval cancer with erlotibnib (an EGF receptor type 1 inhibitor) resulted in kidney failure in 3 patients during clinical trials [141]. The cause of that effect was not reported by the authors but suggests that either the vulval cancer resulted in a coincidental effect, or the monoclonal antibody itself damaged the kidney [140].

Currently, there is no available data on the potential relationship between kidney dysfunction and oviductal cancer. The reason for this may be because this form of cancer is the rarest of all gynaecological cancers, or because it is often also included in with ovarian cancers, since it is thought that some forms epithelial ovarian cancers arise from the distal end of the oviduct [142].

Kidney dysfunction and implications for anticancer drug selection and dosing

The practicing gynaecology oncologist needs to be aware that systemic anticancer treatment can damage the kidney [143] and so exacerbate an undiagnosed or diagnosed issue that may result in AKI or CKD [74,144]. It has long been appreciated that the kidneys can be directly affected (e.g. damage of the proximal convoluted tubule in the presence of cisplatin or gemcitabine) or indirectly affected (e.g. through nephron-induced damage by methotrexate crystal deposition or tumour necrosis syndrome) [145-147] where blockage of the urinary tract can lead to hydronephrosis, especially in women with cervical cancer [42,44,120,148,149].

It is also known that prior to medication with chemotherapeutic agents, the cancer patient's renal function should be known [150,151]. Studies performed in Australia and Poland, indicate that this is not always performed [75,152]. The current recommendation in many centres is for a nephrologist with a special interest in oncology should be a member of the multi-disciplinary team responsible for the cancer patient's treatment. This quantum change in strategy is supported by the new discipline of onconephrology [153,154], where the key concept presented is that the damage of the target cancerous organ (gynaecological cancer) and the kidney is bi-directional [153,154], with effective chemotherapeutic agents that destroy or damage

the tumour resulting in either tumour metabolites or tumour casts being circulated to the kidney to cause AKI [155]. Because of these observations, several alterations to the standard cancer treatment regimens are advised [40,79] such as the use of surtuins to mitigate the effect of cisplatin-induced nephrotoxicity [156] or the use of glucarpidase (a bacterial enzyme) to reduce the renal toxicity of methotrexate [157]. Additional changes to the dosing of such anticancer drugs to prevent tumour lysis syndrome and the impeding mortality associated with it [158] are recommended.

Because many anticancer drugs cause nephrotoxicity, due to the impaired renal elimination of the drug (even in a patient without incipient kidney dysfunction), many anticancer drugs are administered at a lower concentration that was originally intended, which may be problematic. For example, in the IRM-1 study [159], 79.9% of the cancer patients received at least one dose that was reduced for that patient, which essentially made the drug ineffective. This led to new guidelines and prescription books related to anticancer dosing for cancer patients with renal dysfunction, which should be followed.

Conclusions

Currently available data suggest (in general) that a reduced eGFR (as a measure of renal dysfunction), may be associated with many types of cancer and has led to the recent emergence of onconephrology as a separate sub-specialty [160] with some gynaecological cancers (principally cervical and endometrial) being included in the onconephrology database. The suggestion is that kidney disease (especially CKD) and different types of cancer (including gynaecological cancers) is bidirectional with kidney function affecting the cancer, and the cancer affecting the kidney resulting in the observed lower eGFR [154]. The association is more evident for endometrial cancers with several research outputs showing a positive correlation. However, a better understanding of the role of eGFR, and more globally, kidney function and dysfunction in gynaecological cancers requires further research to unravel this complex interaction.

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