

# Chapter 17: Cancer Screening in ESRD

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## INTRODUCTION

The American Cancer Society recommends specific age-related screening examinations for colorectal, breast, and cervical cancer and suggests that individuals discuss their risk factors and screening for prostate and lung cancer with their primary care physician (Table 1) (1). Such recommendations are incorporated into guidelines for periodic adult health care for the general population. Cancer screening for any individual is predicated on the risk of developing cancer and the likelihood that the screening test will detect the cancer. An individual's expected survival is also an integral factor in cancer screening. If expected survival is low, then the cost-effectiveness of routine cancer screening in average-risk individuals argues against screening because the patient will probably die before cancer develops and is detected. In the ESRD population, therefore, when considering routine cancer screening, it is important to ask the following: 1) is there an increased risk of cancer in this patient group?; 2) are screening tests accurate in this population?; and 3) will the patient live long enough for cancer screening to detect a life-threatening disease that can be cured? These issues will be discussed to demonstrate that, because of the high mortality with ESRD, routine cancer screening is not indicated for most patients.

## CANCER RISK IN ESRD

Table 2 shows a summary of the published literature cancer incidence among ESRD patients. The standardized incidence ratio (SIR) is typically used to assess cancer frequency. Viral-mediated cancers like human papilloma virus (HPV)-associated cervical, uterine, and tongue cancer and hepatitis C- and B-associated liver cancer are more common in ESRD patients (2–8). Although there are no clinical data, the SIR for cervical cancer in ESRD patients suggests that young women (and men) with ESRD

should receive the HPV vaccine according to the recommendations in the general population (9). Bladder cancer is also more common in ESRD patients, likely in part due to medications associated with the development or treatment of kidney disease (oral cyclophosphamide use, analgesic use leading to chronic tubulointerstitial disease). These cancers, as well as liver cancer, are more common among Asian ESRD patients (6). Because of the development of acquired cystic disease in ESRD, renal cell carcinoma is also more common among dialysis patients, albeit with a relatively low incidence in most studies (5,7) (Table 2). Routine screening for renal cell carcinoma in chronic dialysis patients remains somewhat controversial but most advocate for individual patient-directed screening based on cost-effectiveness (10,11). The relatively low incidence of renal cell carcinoma in the setting of acquired cystic disease and the low expected patient survival with ESRD argues against routine screening. However, for patients on transplant waiting lists, screening may be advisable and required.

## EFFICACY OF CANCER SCREENING TESTS IN ESRD

Cancer screening is primarily based on imaging techniques or laboratory and histopathologic examinations (Table 1). For most of these evaluations, the positive and negative predictive value of the test has not been assessed in ESRD patients. Due to the presence of vascular calcifications, mammography interpretation in women with ESRD may be more difficult (12,13). The higher rates of gastrointestinal bleeding in ESRD may result in higher fecal occult blood tests than the general population (14). This may actually lead to higher rates of

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**Table 1. American Cancer Society Recommendations for Routine Cancer Screening**

Cancer	Recommended screening
Breast	Yearly mammogram beginning at age 40, continuing as long as in good health Clinical breast examination every 3 years from age 20 to 39 and then yearly for age >40 MRI for high-risk women
Colorectal	Beginning age 50: Flexible sigmoidoscopy every 5 years or colonoscopy every 10 years or double contrast barium enema every 5 years or CT colonography (virtual colonoscopy) every 5 years, with yearly fecal occult blood test or fecal immunochemical test or stool DNA test done every 3 years
Cervical	Begin screening at age 21: 21–29 years: Pap every 3 years; no HPV unless Pap is abnormal; 30–65 years: Pap + HPV every 5 years or Pap alone every 3 years; >65 years: no screening
Prostate	Age 50, discuss pros and cons with MD; age 45 if African American or father or brother with prostate cancer before the age of 65
Lung	No recommendation High risk: consider screening age 55–74 in fairly good health with at least 30–pack-years smoking history and either still smoking or quit within the last 15 years

Individuals with risk factors for specific cancers may need alternate screening protocols and should discuss with their physicians. Adapted from the American Cancer Society website.

colonoscopies in ESRD patients, perhaps resulting in earlier detection of colorectal cancer in ESRD patients compared with the general population (15). There is no information on the reliability of fecal immunochemical or stool DNA testing in ESRD patients. An ongoing study on the performance of fecal occult blood testing in CKD may help to clarify these issues (16).

**Table 2. Cancer incidence in ESRD: Literature summary**

Cancer	SIR	Risk factors in ESRD	References
Renal cell	3.6–24.1	Acquired cystic disease	2–8
Bladder and ureter	1.5–16.4	Analgesic abuse, Balkan nephropathy, oral cyclophosphamide	2,3,5,6,8
Tongue	1.2–1.9	Human papilloma virus	2,3,6
Cervical and uterine	0.9 2.7–4.3+	Human papilloma virus	6 2,3
Liver	1.4–4.5	Hepatitis B and C	2,3,5,6
Thyroid and other	2.2–2.3		2,3,6
Endocrine organs			
Breast (women)	0.8–1.42		3,6,8
Lung/bronchus	0.5–1.28		3,6,8
Colon/rectum	1.0–1.27		3,6,8
Pancreas	1.08		8
Prostate	0.5–1.08		3,6,8

Adapted from reference 25 with additional data and references.

Tumor markers are sometimes used as cancer screening tools and may be affected by ESRD. Total prostate specific antigen (PSA) is probably valid in ESRD patients (17–19), but free PSA and free/total PSA ratios are less useful, as free PSA rises with hemoconcentration and high-flux dialysis membranes affect its clearance (18,19). For unclear reasons, prostate cancer is the only tumor diagnosed at a later stage in ESRD patients compared with the general population (15). Prostate cancer has generally not been more common in ESRD patients (2–7). However, a recent study found an SIR of 1.06 for prostate cancer (8), raising the issue of an increasing incidence of this cancer among ESRD patients. Controversy continues about screening for prostate cancer in the general population (Table 1). Most tumor markers are unreliable in ESRD patients; they are generally glycoproteins with high molecular weight that are rarely removed by dialysis and rise with hemoconcentration, yielding false-positive results in ESRD. For example, cancer antigen 125 (CA-125), a tumor marker for ovarian cancer, is produced by mesothelial cells, and patients with any serosal fluid (pleural effusion, ascites) will have elevated levels. This is especially applicable to patients on peritoneal dialysis, making CA-125 less useful in all ESRD patients, particularly those on peritoneal dialysis.  $\beta$ -human chorionic gonadotropin and  $\alpha$ -fetoprotein, as well as total PSA, are probably reliable in ESRD patients.

The recently published clinical trial on the cost-effectiveness of computed tomography (CT) screening for lung cancer in high-risk individuals reported a 20% reduction in mortality over a 4-year period in patients undergoing three annual CT exams at a cost of \$81,000 per quality-adjusted life-year and incremental cost-effectiveness ratios of \$52,000 per life-year gained (20). This study led the US Preventive Services Task Force to assign a B rating to the recommendation that annual low-dose CT scanning be performed as a screen for lung cancer in adults 55–80 years of age with a 30–pack-year smoking history. However, remaining questions about the overall efficacy of this screening method prompted the American Cancer Society (Table 1) to avoid endorsing CT scanning as a cancer screen. The Centers for Medicare and Medicaid, despite initial misgivings (21), have now endorsed lung cancer screening with CT scans. Lung cancer has not traditionally been more common in ESRD patients (2–6), and ESRD patients' reduced survival argues against the adoption of lung cancer screening in this population. Recently, a 1.28 SIR for lung cancer in ESRD patients (8), along with the benefits of CT screening in at-risk individuals (20), suggests additional study may be needed.

### IS CANCER SCREENING APPROPRIATE IN ESRD GIVEN EXPECTED SURVIVAL?

Although survival in ESRD may be improving slightly, it remains poor (22). As noted above, a patient's expected survival is an important factor to consider when weighing the

benefits of cancer screening. Hypothetical modeling done in the 1990s suggested cancer screening in a dialysis patient would on average provide a net gain of 5 days of survival (23). This model was biased toward cancer screening, examining Papanicolaou smears for detecting cervical cancer, mammography as a screen for breast cancer, flexible sigmoidoscopy for colorectal cancer, and digital examination with PSA testing for prostate cancer assuming screening tests were perfectly sensitive and specific and that each detected cancer was instantaneously treated and cured (23). Using this model, the costs per unit of survival benefit provided by cancer screening were 1.6–19.3 times higher among ESRD patients (23). Another study focusing on breast cancer screening in dialysis patients found an absolute reduction in breast cancer mortality of 0.1% with a net gain in life expectancy of 1.3 days (24). Even focusing on the dialysis patient with the best predicted survival (a young black woman without diabetes mellitus) and multiple risk factors for breast cancer, only 250 days of life were estimated to be saved by screening with mammography in another study (25). Such investigations led to the recommendation to perform cancer screening only on dialysis patients assumed to benefit; cancer screening in ESRD should be based on the individual, considering his or her risk factors for cancer, as well as expected survival with ESRD (23–30).

Transplant candidacy also needs to be considered when contemplating cancer screening in ESRD patients. The evaluative process for kidney transplantation includes age- and sex- appropriate cancer screening such as mammography, Papanicolaou smears, and PSA testing. Thus, cancer screening for transplant candidates is generally required. However, ESRD patients will need to be assessed on an individual basis, considering cancer risk factors, transplant status, and, importantly, expected survival to proceed with cancer screening in a cost-effective manner. Table 3 suggests an outline for cancer screening in ESRD patients based on these factors.

## SUMMARY AND CONCLUSIONS

Although bladder cancer and viral-mediated cancers like HPV-associated cervical cancer and hepatitis C- and B-associated liver cancer are more common in ESRD patients, general routine cancer screening in ESRD patients is not recommended. ESRD patients in whom cancer screening should be considered are those with good expected survival, candidates for kidney transplantation, and certain individuals with a high cancer risk and good expected survival. Although acquired cystic kidney disease is associated with an increased risk of renal cell carcinoma, the same general rules apply; routine screening is not recommended for most patients. The tendency may be to implement routine cancer screening protocols in dialysis units, but individualized patient assessment is required for appropriate cancer screening. The emerging model of personalized cancer screening for the general population is being discussed (31) and seems clearly appropriate for those on dialysis.

**Table 3. Suggested cancer screening in ESRD patients: Individualized, considering expected survival, risk factors, and transplant status**

Cancer	Recommended screening
Breast	-Yearly mammogram beginning age 40 and on transplant list Clinical breast examination every 3 years for ages 20–39 and yearly for age >40
Colorectal	Beginning age 50: Yearly FIT or FOBT for those on transplant lists and flexible sigmoidoscopy, colonoscopy, double contrast barium enema, or virtual colonoscopy per transplant evaluation protocols Positive FIT or FOBT will require additional evaluation
Cervical	Begin screening at age 21: 21–65, yearly Pap for those on transplant list; consider HPV DNA and HPV vaccine in transplant candidates
Prostate	Age 50, annual PSA and digital rectal examination for men on transplant list Age 45 if African American or father or brother had prostate cancer before the age of 65
Renal cell	Yearly CT or MRI in patients on dialysis >3 years and on transplant list

For all the above cancers, consider screening in high-risk patients with long expected survival. FIT, fecal immunochemical test; FOBT, fecal occult blood test. Adapted from references 22–29.

## TAKE HOME POINTS

- Viral-associated cancers like hepatitis B- and C-associated liver cancer and human papilloma virus-associated tongue and cervical cancer are more common in ESRD patients.
- Because of acquired cystic disease, renal cell carcinoma is more common in ESRD patients, and exposure to analgesic abuse and oral cyclophosphamide result in an increased incidence of bladder cancer in ESRD patients.
- Due to poor expected survival with ESRD, cancer screening is not appropriate for most dialysis patients. Patients with long expected survival, those on transplant waiting lists, and those with increased cancer risk factors are appropriate candidates for cancer screening.

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## REVIEW QUESTIONS

1. Is the cancer incidence in ESRD patients higher than in the general population?

Answer: Yes, for certain cancers. Virus-associated cancers (liver cancer, cervical cancer, and tongue cancer) and renal cell and bladder cancer (because of risk factors) are more common in ESRD patients. Breast, colorectal, and lung cancer are not more common in ESRD patients.

2. What factors affect the efficacy or cost-effectiveness of cancer screening in general?

Answer: The cancer risk, the effectiveness of the screening test, and the patient's expected survival all affect the efficacy of

cancer screening. Screening is predicated on the patient living long enough to develop a specific cancer and the sensitivity and specificity of the screening test to detect that cancer at a stage when cure is possible.

3. Should routine screening protocols be in place in dialysis units?

Answer: No, routine cancer screening is not cost-effective for most dialysis patients because their expected survival is short. An individualized approach to cancer screening is most appropriate for ESRD patients, considering the patient's specific risk factors for cancer development, transplant status, and expected survival.