

Screening, Diagnosis, and Treatment of Cancer in Long-Term Dialysis Patients

Jean L. Holley

University of Virginia Health System, Nephrology Division, Charlottesville, Virginia

Some have suggested that the American Cancer Society guidelines for cancer screening be applied to patients who are on long-term dialysis and have used cancer screening as a means of assessing delivered preventive health care to patients with ESRD. However, cancer screening is effective only when it leads to survival benefit (usually expressed as days of life saved) without incurring high financial costs. Certain cancers such as human papillomavirus-associated cervical and tongue cancer and urologic malignancies are more common among dialysis patients, yet because the expected remaining lifetime of most dialysis patients is shorter than the time lived to develop malignancy, cancer screening in dialysis patients as applied to the general population is ineffective from the perspective of both cost and survival benefit. Cancer screening in dialysis patients is therefore best provided in an individual patient-focused manner. The occurrence, diagnosis, and treatment of cancer as well as issues related to cancer screening in dialysis patients are discussed.

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Cancer screening in the general population serves as the basis for many clinical practice guidelines and health plan assessments. Screening protocols incorporate risk factors and are included in periodic health assessments (1). Some have criticized the lack of routine cancer screening in the chronic kidney disease and dialysis populations but often without considering the cost-effectiveness of screening these patients (2,3). Although certain cancers are more common among dialysis patients (4–12), the expected remaining lifetime of most dialysis patients is shorter than the time lived to develop malignancy, making cancer screening ineffective from the perspective of both cost and survival benefit conferred (13–17). In addition, malignancy is a relatively rare cause of death in dialysis patients (3,6,17), and early detection has not improved mortality in this population (6). Little is known about the success of cancer treatment in dialysis patients, but clearly the cooperation of dialysis, nephrology, and oncology teams is needed to treat dialysis patients with cancer. Cancer occurrence, screening, and treatment in dialysis patients are reviewed, and recommendations for patient-specific and limited routine cancer screening in dialysis patients are presented.

Cancer Screening in Dialysis Patients

Cancer-related examinations are part of adult periodic health examinations. Health care counseling is an integral part of routine medical care not only to reduce cancer risk that is associated with certain behaviors (*e.g.*, use of tobacco), hereditary predispositions (*e.g.*, breast cancer, intestinal polyposis), occupational exposures, and underlying medical conditions but

also to emphasize preventive measures to reduce cancer risk. Physical examinations are also part of cancer screening (*e.g.*, oral cavity, skin, testes, lymph nodes, thyroid, ovaries) during periodic health examinations. In addition to these general measures, the American Cancer Society recommends screening for breast, colon and rectal, cervical, and prostate cancer with specific age- and risk-adjusted tests (Table 1) (1).

The appropriateness of a screening test depends on disease occurrence in the population, the sensitivity and the specificity of the test to be used, and the efficacy of interventions to alter the expected outcome if screening detects disease. When evaluating cancer screening in dialysis patients, therefore, the occurrence of cancer in the population, the effectiveness of screening tests, and patients' expected survival all need to be considered. Table 2 summarizes the frequency of certain cancers in the dialysis population. In addition to traditional cancer risk factors, dialysis patients are more susceptible to viral-mediated cancers, including human papillomavirus (HPV)-associated cancers such as cervical cancer and carcinoma of the tongue (5). There is also an increased risk for renal cell carcinoma and cancers of urologic transitional cell origin (7,8–12), likely because of the higher frequency of acquired cystic disease of the kidneys and analgesic abuse (4,5,7–12), both recognized risk factors for transitional cell carcinoma of the urologic tract. Epidemiologic studies suggest these cancers may be more common in Asian individuals (7).

In addition to cancer frequency in a population, the efficacy of screening tests needs to be considered to evaluate the effectiveness of cancer screening protocols. Table 1 lists the suggested screening tests in the general population for breast, cervical, colorectal, and prostate cancer. Although the positive and negative predictive value of screening tests have not been validated in dialysis patients, some clinical caveats should be considered when applying these screening tests to dialysis

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Address correspondence to: Dr. Jean L. Holley, University of Virginia Health System, Nephrology Division, Box 800133, Charlottesville, VA 22908. Phone: 434-924-5125; Fax: 434-924-5848; E-mail: jlh4qs@virginia.edu

Table 1. American Cancer Society recommendations for routine cancer screening in the general population^a

Cancer	Screening Recommended	Screening At-Risk Individuals: Discuss with Physician
Breast	Mammogram yearly after age 40 Clinical breast exam yearly at ≥ 40 yr; every 3 yr ages 20s to 30s Breast self-exam option in 20s	Earlier screening, additional tests (<i>e.g.</i> , ultrasound, MRI) More frequent exams
Colon and rectal	Beginning age 50: yearly FOBT or FIT Flexible sigmoidoscopy every 5 yr Yearly FOBT or FIT + flex sigmoid every 5 yr ^b Double contrast barium enema every 5 yr, colonoscopy every 10 yr All positive tests should be followed up with colonoscopy	Personal history of cancer or adenomatous polyps Family history of cancer or polyps in first-degree relative < 60 yr of age or in two first-degree relatives of any age Personal history of chronic inflammatory bowel disease Family history of hereditary colorectal cancer syndrome
Cervical	All women begin yearly Pap test approximately 3 yr after beginning vaginal intercourse but no later than 21 yr of age; newer liquid-based Pap test can be done every 2 yr. Beginning at age 30, women with three normal yearly sequential Pap tests may reduce screening to every 2 to 3 yr or screen every 3 yr with Pap + HPV DNA test. Women ≥ 70 yr of age with three or more normal sequential Pap tests and no abnormal tests in 10 yr may choose to stop screening. Women who have had a total hysterectomy may choose to stop screening unless hysterectomy was done as treatment for cervical cancer or precancer.	Diethylstilbestrol exposure before birth, HIV infection, suppressed immune system (organ transplant, chronic steroid use, chemotherapy) continue annual screening Continue yearly screening for high-risk individuals as noted above
Endometrial	Women who are at risk for hereditary nonpolyposis colon cancer should be offered annual screening for endometrial cancer with endometrial biopsy beginning at age 35.	
Prostate	Annual PSA blood test and digital rectal exam beginning at age 50 for men with at least 10-yr life expectancy.	High-risk men (black, history in first-degree relative diagnosed before age 45) begin screening at age 45; if multiple first-degree relative affected at early age, begin screening at age 40. Provide information to all men about known and uncertain benefits, limitation, harms of early detection and treatment.

^aAdapted from reference (1). FIT, fecal immunochemical test; FOBT, fecal occult blood test; HPV, human papillomavirus; MRI, magnetic resonance imaging; Pap, Papanicolaou; PSA, prostate-specific antigen.

^bThe combination of yearly FOBT or FIT and flexible sigmoidoscopy every 5 yr is preferred over either of these options alone.

patients. For example, mammography in women with ESRD is likely to be confounded by vessel calcifications, which are significantly more common than in the general population (18,19). Radiologic interpretation of these calcifications requires appropriate historical information to avoid unnecessary procedures that are based on an initial mammogram. Higher rates of positive tests are observed with stool hemoccult testing in dialysis patients, primarily because a higher incidence of gas-

trointestinal blood loss of variable causes occurs in this population (20). The likelihood of a positive hemoccult test also increases as chronic kidney disease progresses (21). Because hemoccult testing alone is not sufficient for colorectal cancer screening (Table 1) and because positive hemoccult tests require additional testing, using stool hemoccult to screen for colon and rectal cancer in dialysis patients is appropriate as long as a higher rate of colonoscopies is expected.

Table 2. Reported frequencies of cancers in the ESRD population^a

Cancer	Risk Factor	Relative Risk	Reference
Renal cell	Acquired cystic disease	1.5 to 25% incidence; 3.6 to 24.1 SIR	(4,5,7–9,11,12,27,28)
Bladder and ureter	Balkan nephropathy analgesic abuse; oral cyclophosphamide	1.50 to 16.4 SIR	(4,5,7)
Thyroid and other endocrine organs		2.28 SIR	(4,5)
Cervical, uterine	HPV	2.7 to 4.3 SIR ^b	(4,5,8)
Prostate		0.93 SIR ^b ; 1.8 to 2.1	(4,5,8,10)
Liver	Hepatitis C and B	1.4 to 4.5 SIR ^b	(4,5,7)
Tongue	HPV	1.9 SIR ^b	(4,5)
Multiple myeloma		4.0 SIR ^b	(4,5)

^aSIR, standardized incidence ratio.

^bAverage of three different countries.

Tumor markers are used to follow the clinical course of certain cancers and also as cancer screening tools. Prostate-specific antigen (PSA) is a tumor marker that is used as a screening test, usually in combination with digital rectal and/or ultrasound-guided examination (Table 1). Evaluating tumor markers in dialysis patients can be difficult (see the Tumor Markers in Dialysis Patients section), but total PSA is probably valid in patients with ESRD (22–24); free PSA and free/total PSA ratios in dialysis patients are less useful because free PSA tends to be elevated in association with hemoconcentration (23), and its clearance is affected by high-flux dialysis membranes (24).

Although nearly 95% of those who receive a diagnosis of lung cancer die from it (25), the American Cancer Society does not currently recommend routine screening for lung cancer (1). The effectiveness of annual screening with spiral computed tomography (CT) to detect stage I lung cancer in cigarette smokers has been shown (26). A survival benefit of patients with stage I lung cancer that is detected on screening has also been observed, and screening with spiral CT is suggested to be cost-effective (25). Adoption of routine lung cancer screening protocols, however, is not yet widespread or endorsed by the American Cancer Society.

The third factor to consider in determining the cost-effectiveness of cancer screening is the ability of therapeutic intervention to alter the disease process and prognosis. Therefore, the expected survival of the population with and without cancer is an important consideration when contemplating routine cancer screening in chronic dialysis patients. Multiple studies have demonstrated the ineffectiveness of routine cancer screening using mammography, stool hemoccult testing and flexible sigmoidoscopy, Papanicolaou smears, and prostate examination with PSA in chronic dialysis patients (13–15). Estimated days of life saved by cancer screening is a function of life expectancy and lifetime risk for developing a cancer that will cause death. Dialysis patients' high expected mortality results in nonsignificant days of life saved in all hypothetical scenarios of cancer screening (13–15). For example, screening mammograms in black women who do not have diabetes and are on dialysis

saved fewer than 50 d of life, even when multiple breast cancer risk factors were present (17). The best case assumptions (multiple breast cancer risk factors and no diabetes in a young woman who is on dialysis) suggest that only 250 d of life could be saved by screening mammography (17). In a study by Chertow *et al.* (19), a typical cancer screening program (Table 1) resulted in a net gain in life expectancy of 5 d or less in dialysis patients. Moreover, the financial costs per unit of survival benefit conferred by cancer screening were 1.6 to 19.3 times greater among patients with ESRD (19). Screening is least efficient and cost-effective in patients who are 50 to 70 yr of age and among white patients and women (17–20). In addition, the predictive value of screening tests has not been validated in dialysis patients. Therefore, a focused, individualized patient approach to cancer screening rather than dialysis unit-wide policies for cancer screening seems most appropriate (13–17) (Table 3).

Acquired Cystic Disease and Renal Cell Carcinoma in Dialysis Patients

Cancer registry studies report higher frequencies of urogenital cancer in patients with ESRD in large part because patients with ESRD carry risk factors for these cancers (4–12) (Table 2). One risk factor is acquired cystic disease of the kidney. After 3 yr on dialysis, most patients will develop acquired kidney cysts that are visible on ultrasound or CT imaging. The incidence of acquired cystic disease rises with increasing time on dialysis, and >50 to 80% of patients are affected after 10 yr (27–29). Acquired cystic disease is associated with a 1.6 to 7% incidence of renal cell carcinoma (9,27). Because the development of acquired kidney cysts in patients with ESRD corresponds with dialysis duration and because renal cell carcinomas develop in approximately 2% of individuals with acquired cysts, some have argued for routine screening for renal cell carcinoma in patients who are on dialysis for >3 yr (28). However, the relatively low incidence of renal cell carcinoma coupled with the high overall mortality of patients with ESRD and the need

Table 3. Considerations for cost-effective cancer screening in dialysis patients: Individual-focused screening with attention to risk factors, expected survival, and transplant status

Cancer	Screening to Consider
Breast	Mammogram yearly at age >40 and on transplant waiting lists Clinical breast exam yearly at ≥40 yr; every 3 yr ages 20s to 30s; breast self-exam option in 20s
Colon and rectal	Consider screening in high-risk individuals with long expected survival Beginning age 50: yearly FOBT or FIT for those on transplant waiting lists and flexible sigmoidoscopy, colonoscopy, or double contrast barium enema as suggested by transplant evaluation protocols Consider screening in high-risk individuals with long expected survival
Cervical	All positive FOBT or FIT may need to be followed up with colonoscopy Yearly Pap test approximately 3 yr after beginning vaginal intercourse and no later than 21 yr of age. Newer liquid-based Pap test can be done every 2 yr HPV DNA and HPV vaccine to be considered, especially in transplant candidates Yearly Pap test in those on transplant waiting list and those with risk factors and long expected survival
Prostate	Annual PSA blood test and digital rectal exam beginning at age 50 for men on transplant waiting list
Renal cell	Consider screening in high-risk individuals with long expected survival Yearly CT or MRI in patients on dialysis >3 yr and on transplant waiting list

^aAdapted from references 1,7,8–17,27–30,41–44. CT, computed tomography.

for CT or magnetic resonance imaging for effective screening in this population has prompted others to suggest that routine screening is not cost-effective (29). A decision analysis found that screening could lead to a 1.6 yr gain in life expectancy over a 25-yr period provided that only young patients with a long life span were screened (30). A middle ground is often adopted by dialysis programs whereby patients who are active on transplant waiting lists undergo yearly screening and those who are not on transplant lists are not routinely screened.

Diagnosis of Cancer in Dialysis Patients

Tumor Markers in Dialysis Patients

PSA is the tumor marker that is most widely used as a cancer screening test. Most tumor markers are glycoproteins that have relatively high molecular weight (5000 to 180,000 kd) and are rarely removed effectively by dialysis. Levels may also rise with hemoconcentration (31–33). Therefore, many tumor markers yield false-positive results in dialysis patients and are of limited clinical use. Table 4 lists the common tumor markers and their efficacy in dialysis patients. Cancer antigen 125 is a tumor marker for ovarian cancer but is also produced by mesothelial cells (34) and has been reported to be a functional marker for mesothelial cell mass and transport characteristics in patients who are on peritoneal dialysis (35). However, cancer antigen 125 is less useful as a tumor marker in dialysis patients because any serosal fluid (pleural effusion, ascites, etc.) will cause elevated levels (36). α -Fetoprotein, β -human chorionic gonadotropin, and PSA are the most useful tumor markers in patients with ESRD.

Imaging Studies in Dialysis Patients

Radiologic imaging studies are integral to the evaluation of malignancy, but imaging in dialysis patients raises some specific issues. As noted, vascular calcification in women who are on dialysis may affect interpretation of mammograms (18,19). Maintenance of residual kidney function in dialysis patients may influence the choice of radiologic procedure as well as preprocedure strategies to reduce the risk for contrast-induced acute renal failure. Although magnetic resonance imaging with low dosages of gadolinium was thought to be safe in patients with chronic kidney disease, especially when dialysis was used for poststudy gadolinium removal (37,38), there is some concern that sclerosing fibrosing dermopathy in dialysis patients may be associated with gadolinium (39,40). Postimaging dialysis to remove gadolinium in some patients should perhaps be considered. In addition, acute renal failure from acute tubular necrosis can occur with gadolinium exposure (41). Further study of this issue is needed.

Cervical Cancer Screening and Prevention: HPV

As noted in Table 1, HPV DNA testing may complement the traditional Papanicolaou test for cervical cancer screening and can be performed in liquid-based cytology systems (42). Epidemiologic studies show that HPV DNA is present in nearly all cervical cancers (43). Positive HPV DNA tests are more sensitive (but less specific) than exfoliative cytology in predicting women who are at risk for cervical cancer (42). An HPV vaccine has been developed and is recommended in female individuals who are aged 9 to 26 (44,45). The vaccine protects against HPV

Table 4. Tumor markers in ESRD^a

Reliability	Tumor Marker	Notes
Reliable in dialysis patients	α -fetoprotein <i>Helicobacter pylori</i> PSA	Total PSA is not cleared by dialysis membranes; free PSA is cleared by high-flux membranes; free PSA and total:free PSA reliable only with low-flux membranes (24); normal % free PSA do not apply to dialysis patients (23)
Interpret with caution, often elevated in dialysis patients	β -human chorionic gonadotropin CA 19-9, CA 125, CA 50	Good specificity and of some clinical value; often moderately elevated with peritoneal, pleural, or pericardial fluids (36)
High false-positive in dialysis patients	Carcinoembryonic antigen Squamous cell carcinoma antigen Neuron-specific enolase	

^aCA, cancer antigen.

types 6, 11, 16, and 18 (responsible for 70% of cervical cancers and 90% of genital warts), but because additional HPV strains can cause cervical cancer, the recommendations for cervical cytologic screening remain unchanged. The vaccine is most effective when administered before the onset of sexual activity but can be given after HPV exposure, albeit with less effectiveness. Prophylactic HPV vaccine has not been tested in patients with chronic kidney disease, so its efficacy is unknown. However, it should be safe in transplant patients as well as patients with ESRD. Therapeutic use of HPV vaccine awaits additional study (42).

Treatment of Cancer in Dialysis Patients

Once diagnosed, cancer in a dialysis patient is generally treated as in the nondialysis patient with appropriate consideration of the renal clearance, dosing, and dialyzability of chemotherapeutic agents. Communication and cooperation among the dialysis and oncology teams is vital. In some cases, dialysis must be precisely timed in conjunction with chemotherapy administration to avoid toxicity. Few pharmacodynamic data have addressed chemotherapeutic agents in dialysis patients. Most studies consist of case reports and suggest that dialysis patients often tolerate standard treatment (46). Radioactive iodine has the added issue of dialysis-provider safety to be considered. The assistance of experts in radioactive safety will be required in such cases (47). The metabolism and excretion of the drug to be used and appropriate dosage modification will need to be considered by the treating team.

Few data that address the response of dialysis patients to cancer treatment are available. It is interesting that there are three reports on the outcome of dialysis patients who underwent treatment for lung cancer (48–50). Dialysis patients who underwent lung resection had a higher rate of postoperative

complications (*e.g.*, hyperkalemia, arrhythmia, pulmonary complications) than nondialysis patients, but mortality was not different (48–50). The sparse available literature suggests that dialysis patients should not be denied usual treatments for lung cancer. One study that addressed different treatment strategies for patients with ESRD and transitional cell cancers suggested that dialysis patients have higher recurrence rates of upper urinary tract cancers than nondialysis patients (51). These authors therefore recommended one-step bilateral nephroureterectomy and radical cystectomy in dialysis patients with transitional cell carcinoma (51). Precise recommendations for treating dialysis patients with cancer can be made only when data on prognosis become available; the lack of clinical trials in this population precludes definitive recommendations. Individualized treatment through collaboration of surgeons, oncologists, nephrologists, and dialysis units is necessary.

Conclusion

Although it is tempting to apply cancer screening protocols that are recommended for the general population to dialysis patients, the poor expected survival of many dialysis patients argues against this approach. Multiple investigators have shown that routine cancer screening in dialysis patients is not effective either in days of life saved or financially and is clinically misguided (13–17). An individualized approach to cancer screening in dialysis patients is required and should be based on the patient's cancer risk factors, expected survival, and transplant status. Surveys that address the effectiveness of cancer screening by dialysis units do a disservice to the nephrology community by failing to address the ineffectiveness of applying general screening practices to this special population. Certain cancers are clearly more common among dialysis patients (Table 2) and may influence dialysis unit screening practices. As

the dialysis population ages, we may see increasingly higher cancer rates in these patients. This will force nephrologists to confront their patients' mortality, quality of life, and options for palliative *versus* curative care to an even greater extent.

Disclosures

None.

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