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REVIEW

Screening for colorectal, breast, and cervical cancer in the elderly: A review of the evidence

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ABSTRACT: There is general consensus that screening can reduce mortality from colorectal, breast, and cervical cancer among persons in their 50s and 60s. However, few screening trials have included persons over age 70 years. Therefore, indirect evidence must be used to determine when results in younger persons should be extrapolated to older persons. In this review, we focus on cancer screening tests that are well accepted in younger persons (mammography, Papanicolaou smears, and colorectal cancer screening) and discuss the strength of inference concerning benefits and harms of screening older persons. Some aspects of aging favor screening (eg, increased absolute risk of dying of cancer) whereas other aspects do not (eg, decreased life expectancy). Age also affects the behavior of some cancers (eg, increases the proportion of slow-growing breast cancers) and affects the accuracy of some screening tests (eg, increases the accuracy of mammography; decreases the accuracy of sigmoidoscopy). These effects make the application of evidence in younger populations to older populations complex. However, given the heterogeneity of the elderly population, there is no evidence of one age at which potential benefits of screening suddenly cease or potential harms suddenly become substantial for everyone. Therefore, characteristics of individual patients that go beyond age should be the driving factors in screening decisions. For example, persons who have a life expectancy less than 5 years or persons who would decline treatment should generally not be screened. Decisions to either continue or discontinue screening in the elderly should be based on health status, the benefits and harms of the test, and preferences of the patient, rather than solely on the age of the patient.

There is substantial evidence that screening for colorectal, breast, and cervical cancer reduces cancer mortality among persons in their 50s and 60s,[1-9] although few screening trials have included persons over age 70. There are no randomized trials in any age group supporting screening for other cancers, such as prostate or ovarian cancer.[10] Therefore, this review focuses on screening tests that are well accepted in younger adults and addresses the question: "Should evidence of screening efficacy in younger persons be extrapolated to older persons or should clinicians stop screening persons who are older than patients who were included in the screening trials?" To assess the appropriateness of extrapolation, the following issues will be considered: Do differences in the behavior of cancers in older people reduce the benefit of early detection and treatment? Does the ac-

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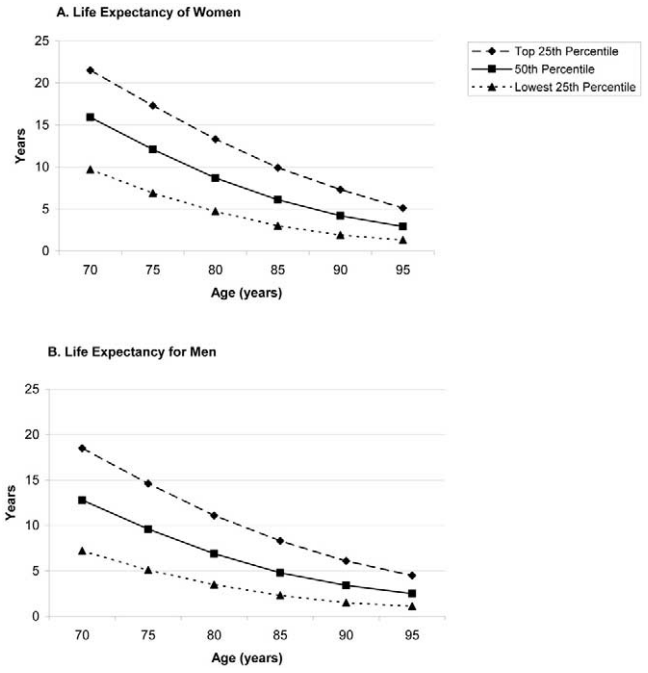

Figure Upper, middle, and lower quartiles of life expectancy for older women and men. For example, 25% of 80-year-old women will live more than 13 years, 50% will live at least 9 years, and 25% will live less than 5 years. Older persons with heart failure, end-stage renal disease, oxygen-dependent chronic obstructive lung disease, dementia, or severe functional dependencies in activities of daily living would fall into the lowest quartile of life expectancy and in general would be unlikely to benefit from screening. Elderly patients without comorbid conditions or with a functional status that is considerably better than the average for their age are likely to be in the upper quartile.[13] Data from Life Tables of the United States, 2001.[15]

curacy of screening tests change in older people? Do individual differences among patients alter the likelihood of benefit of screening for cancer?[11]

Screening for colorectal, breast, and cervical cancer will be discussed in this context by reviewing evidence from clinical trials that included older persons, as well as indirect evidence about the effects of advancing age on the potential benefits and harms of screening. The main benefit of screening is the reduction in cancer mortality experienced by a few people whose early-stage disease is detected and treated, which otherwise would have been lethal in their remaining lifetime.[12] The harms of screening, which may affect anyone, include complications from screening tests or evaluation of false-positive test results, detection and treatment of clinically inconsequential disease that never would have produced symptoms during a person's lifetime, and psychological distress.[13] How age affects these benefits and harms is complex because some aspects of aging favor screening (eg, cancer mortality increases), whereas other aspects argue against screening (eg, life expectancy decreases).[13,14] In addition, the elderly population is heterogeneous (Figure).[15] Although it is impossible to predict the exact life expectancy of a person, a consideration of health and functional status allows for better estimations of life expectancy than does age alone.[16,17] Estimates of life expectancy in turn factor into whether the harms of screening outweigh the benefits.[13]

Colorectal cancer

Evidence of benefit

For colorectal cancer screening, fecal occult blood testing has the strongest evidence of benefit in elderly patients.[18,19] Three randomized trials, including more than 40 000 persons aged 70 to 80 years, demonstrated that screening every 1 to 2 years reduced colorectal cancer incidence and death (Table 1). For example, 2 European trials of biennial, unhydrated fecal occult blood testing found that screening reduced colorectal cancer mortality for persons aged 45 to 75 years by 15% to 18% over 8 to 13 years.[20-23] A trial in the United States demonstrated that annual rehydrated fecal occult blood testing also reduced the incidence of colorectal cancer for persons aged 50 to 80 years by 20% (95% CI: 10% to 30%) after 18 years of follow-up.[24,25] Biennial screening decreased the incidence by 17% (95% CI: 6% to 27%). The efficacy of screening was independent of advancing age, although no subgroup analyses of older persons have been published.

Additional tests for colorectal cancer screening include flexible sigmoidoscopy, colonoscopy, and double-contrast barium enema. The efficacy of sigmoidoscopy is supported by several well-designed case-control studies.[18,19] The study by Selby et al, which included patients aged 45 to 91 years, found rigid sigmoidoscopy was associated with a 59% reduction in mortality from cancer that was within reach of the sigmoidoscope (adjusted odds ratio (OR) = 0.41; 95% CI: 0.25 to 0.69).[26] This protective effect did not differ according to age at diagnosis and is estimated to persist for 6 to 10 years. Colonoscopy also has a long-lasting protective effect. A case-control study, in which almost half of the patients were over age 70, found that patients who died of colorectal cancer were less likely to have had a colonoscopy in the prior 10 years (OR = 0.43; 95% CI: 0.30 to 0.63).[27] No randomized trials have examined the effectiveness of barium enema in reducing the incidence of or death from colorectal cancer, and studies of its accuracy are of poor methodological quality.[19]

Evidence of harm

All screening tests have false-positive results (Table 1). For example, approximately 86% to 98% of trial participants who had a positive fecal occult blood test result did not have colorectal cancer after further evaluation but were exposed to the potential complications of colonoscopy.[20,22,24] Colonoscopy is also the standard evaluation for polyps detected by sigmoidoscopy or barium enema.[18] In a large prospective cohort study, which included 600 veterans aged 70 to 75 years, major complications, including perforation,

Table 1 Randomized trials of cancer screening that included patients over age 70 years

Study characteristics	Hardcastle et al[20,21] (United Kingdom)	Kronborg et al[22,23] (Denmark)	Mandel et al[24,25] (United States)	Tabar et al[45,51] (Swedish Two County)
Cancer test	Colorectal fecal occult blood test (unhydrated)	Colorectal fecal occult blood test (unhydrated)	Colorectal fecal occult blood test (rehydrated)	Breast mammography
Test frequency	Biennial	Biennial	Annual or biennial	33 months (ages 50+)
Participants, n	150 251	61 933	46 551	133 065
Age range, years	45-74	45-75	50-80	40-74
Participants ≥70 years, n (%)	22 659 (15)	9,631 (16)	8,011 (17)	17 646 (13)
Follow-up, years	8	13	18	20
Relative risk of cancer mortality with screening (95% CI) (all ages)	0.85 (0.74-0.98)	0.82 (0.69-0.97)	0.67 (0.51-0.83) (annual) 0.79 (0.62-0.97) (biennial)	0.68 (0.59-0.80)
Persons ≥70 years	Similar	Similar	Similar	0.76 (0.44-1.33)
Cancer deaths prevented/1000 persons screened*	0.8	1.8	4.6 (annual) 2.9 (biennial)	2.2
Number needed to screen to prevent 1 cancer death*	1250	555	217 (annual) 344 (biennial)	465
Time from initiation of screening until onset of mortality benefit, years*	5	5	5	4-5
False-positive results/1000 persons screened†	19	8	96	44
Complications*	5 perforations; 1 major bleed	Not stated	4 perforations; 11 serious bleeds	Not stated

*Data are reported for all participants over the length of trial follow-up because screening trials do not present data by age subgroups.

†False-positive rate calculated as the percent of positive tests during the first round of screening that were not associated with cancer after further evaluation. This rate is calculated from data from all trial participants because the screening trials do not present data by age subgroups.

bleeding, stroke, myocardial infarction, Fournier gangrene and thrombophlebitis, occurred in 3 of 1000 screening colonoscopies.[28] Flexible sigmoidoscopy has fewer complications than colonoscopy, with perforations occurring in less than 0.1 of 1000 examinations. Serious complications are estimated to occur in 0.04 of 1000 barium enemas.[19]

Screening may also lead to polypectomy or surgery to treat inconsequential disease that never would have caused symptoms during a patient's lifetime. In fact, very few adenomatous polyps (<10%) are destined to progress to cancer over 10 years.[29,30] Although the United Kingdom trial reported that fecal occult blood testing rarely led to surgery for inconsequential disease,[31]autopsy studies suggest the potential for more sensitive tests to detect inconsequential disease may be substantial. Approximately 10% to 33% of older persons have polyps, and 2% to 3% have incidental colorectal cancer discovered on autopsy.[3] It is unknown what percentage of these inconsequential lesions would have been detected if these persons had undergone screening during their lifetimes.

Finally, all colorectal cancer screening tests may cause psychological distress, which may range from the alarm of false-positive results to the stress and discomfort of the bowel preparation or screening test.[32,33] The severity and duration of distress varies, although the greatest anxiety for many persons occurs while waiting to undergo further evaluation after a positive test result.[32]

Extrapolating benefits and harms of screening to older patients

Randomized trials of fecal occult blood testing provide direct evidence of the efficacy of screening in older persons. However, these trials do not address the benefit of screening persons over age 80 years or how life expectancy may change the benefit-to-harm ratio of screening. Instead, clinicians must consider indirect evidence (Table 2) to determine how advancing age affects the likelihood of benefit or harm from screening.

Advancing age does not cause colorectal cancer to become more indolent or less responsive to surgery or chemotherapy.[34] Localized colorectal cancer in older persons responds to treatment and is associated with less morbidity and better survival than advanced disease.[35]

Advancing age increases the absolute risk of advanced neoplasia in the right half of the colon (5.6% for persons over age 65 years compared with 0.8% for persons aged 50 to 54 years), thereby decreasing the sensitivity of sigmoidoscopy, which examines only the left half of the colon.[36] Therefore, screening strategies that evaluate the entire colon are often recommended for older persons.[28,36] Fecal occult blood testing can detect curable cancers throughout the colon. However, its sensitivity is low in all age groups (30% to 50%).[37] Colonoscopy is the most sensitive and specific test, although it can be technically more difficult in older

Table 2 Questions to consider when deciding whether to extrapolate results of cancer screening trials to an older patient[11]

Questions	Colorectal cancer	Breast cancer	Cervical cancer
Are there differences in the behavior of cancers in older people that reduce the benefit of early detection/treatment?	No	Yes—Higher proportion of slow-growing cancers	No
Are there differences in the accuracy of screening tests in older people that make tests more likely to miss cancer?	Yes—Flexible sigmoidoscopy becomes less sensitive No—Fecal occult blood tests and colonoscopy	Yes—Clinical breast exam may be less sensitive No—Mammography is more sensitive	Yes—Pap smear may be less sensitive
Are there differences in individual characteristics of older people that:			
Reduce the likelihood of benefit from screening?	Yes—Limited life expectancy; serious comorbidity	Yes—Limited life expectancy; serious comorbidity	Yes—Limited life expectancy; history of normal Pap smears; no cervix
Increase the likelihood of benefit from screening?	Yes—Older age; inflammatory bowel disease; history of multiple or large colorectal adenomas; lack of prior screening	Yes—Older age; family history of breast cancer; longer estrogen exposure (endogenous or exogenous); lack of prior screening	Yes—Lack of regular Pap screening

persons because of changes in elasticity of the bowel and increasing diverticulosis.[19,38]

Individual patient characteristics are the most important factors affecting the likelihood of benefit versus harm of screening. In addition to advancing age, inflammatory bowel disease and a history of multiple or large colorectal adenomas increase the absolute risk of developing and dying from colorectal cancer, which increases the chance to benefit from screening.[39,40] Conversely, the chance to benefit is decreased for patients with serious comorbidity or a history of prior normal screening examinations.[41,18] For example, cardiopulmonary disease and impaired functional status increase the risk of complications from colonoscopy and increase mortality from surgeries to treat colorectal cancer.[42-44] The long natural history of the adenoma-carcinoma sequence and trials demonstrating cancer mortality does not begin to decrease until 5 years after the start of screening also suggest that patients who have a life expectancy less than 5 years are more likely to be harmed from screening than to benefit.[13]

In summary, most guidelines do not recommend using upper age cutoffs to decide when to stop screening for colorectal cancer (Table 3). Rather, most guidelines recommend that the decision to discontinue screening should be individualized, based on whether an older person has characteristics that considerably decrease the benefit-to-harm ratio of screening (eg, limited life expectancy or conditions that increase the risk of colonoscopy).

Breast cancer

Evidence of benefit

The evidence that breast cancer screening benefits older women is not as strong as that for colorectal cancer screening. Of 8 randomized trials of mammography, the Swedish Two County Study was the only trial to include women over age 70 years.[45] However, older women were invited to only two rounds of screening, and subgroup analyses did not show a significant reduction in breast cancer mortality for women aged 70 to 74 years (Table 1). When analyses included women aged 40 to 74 years, this 7-year trial showed a significant (32%) reduction in breast cancer mortality in the screened group after 20 years of follow-up.[46] In fact, all randomized trials that included women aged 50 to 69 years have consistently shown protective effects from mammography.[47,48] Other breast cancer screening tests include clinical breast examination and breast self-examination. However, there are no data from randomized trials to indicate that these tests, without accompanying mammography, reduce mortality from breast cancer in any age group.[49,50]

Evidence of harm

In the Swedish Two County Study, 88% of women with a positive mammogram during the first round of screening did not have cancer (Table 1).[51] More recent Medicare data sug-

Table 3 Guideline recommendations for cancer screening in the elderly

Cancer site	Test	USPSTF guideline	ACS guideline	AGS guideline
Colorectal	Fecal occult blood test (annually) and/or sigmoidoscopy (every 5 years) or colonoscopy (every 10 years) or double-contrast barium enema (every 5 years)	Screen all adults ≥50 years of age. Discontinuing screening is reasonable in persons whose age and comorbid conditions limit life expectancy.[1]	Screen all adults ≥50 years of age. Discontinuing screening is reasonable in persons with severe comorbidity that would preclude treatment.[2]	Screen all adults ≥50 years of age. Persons too frail to undergo colonoscopy and persons with short life expectancy (3-5 years) should not be screened.[3]
Breast	Mammography (every 1-2 years) with or without clinical breast exam (annually)	Screen all women ≥40 years of age. Women with comorbid conditions that limit life expectancy are unlikely to benefit from screening.[4]	Screen all women ≥40 years of age, continuing for as long as a woman is in good health and would be a candidate for treatment.[5]	Screening should continue for older women who have a life expectancy ≥4 years.[6]
Cervical	Pap smear (every 1-3 years)	Discontinue screening in women who have had a total hysterectomy and in women >65 years of age who are not at high risk for cervical cancer and have had adequate recent normal Pap smears.[7]	Immunocompetent women >70 years of age who have had ≥3 normal Pap smears in a row and no abnormal results within 10 years may elect to stop. Screening may be stopped in women who have had a total hysterectomy and women with severe comorbid illness.[8]	It is acceptable to stop screening women >70 years of age who have had ≥2 normal Pap smears since age 60 years and women who have a short life expectancy or would be unable to tolerate treatment.[9]

ACS = American Cancer Society, AGS = American Geriatrics Society, Pap = Papanicolaou, USPSTF = United States Preventive Services Task Force.

gest that for every 1000 women older than 70 years who undergo screening mammography, 77 to 86 will have a positive result, and approximately 86% of these positive mammograms will be false-positives.[52] These women are exposed to follow-up testing, which usually involves diagnostic mammography and biopsy. Biopsy has a low complication rate, which includes infection and scarring.[53] Clinical breast examinations and breast self-examinations, both of which are less specific than mammography, can also lead to follow-up testing for false-positive results. In a large US series of clinical breast examinations, 3.9% of examinations performed on asymptomatic women were abnormal, but 97% of these women did not have cancer after further evaluation.[54]

Screening may also detect inconsequential disease that never would have come to clinical attention had the person not been screened. For example, approximately 1 in 1000 mammograms performed in women aged 70 to 84 years will detect ductal carcinoma in situ, a noninvasive form of breast cancer with an uncertain natural history.[55] Whether the majority or minority of untreated ductal carcinomas in situ will progress to invasive cancer and over what time interval is controversial, so most women undergo surgery.[56] In a series of autopsy studies, the median prevalence of ductal carcinoma in situ at death was 9% among women not known to have breast cancer, whereas incidental invasive breast cancer was found in 1.3%.[57] Women who have surgery for disease that would never have caused symptoms suffer harm from screening.

Finally, a positive screening test may result in psychological distress that may persist even after normal follow-up examinations.[58,59] Screening mammography and follow-up procedures may be especially burdensome or frightening to frail elderly women who have cognitive or functional impairments.[60,61]

Extrapolating benefits and harms of screening to older patients

Although randomized trials have proven the efficacy of screening mammography for women aged 50 to 69 years,

the trials do not provide direct evidence for or against screening women older than age 70 years.[62] Therefore, clinicians must consider indirect evidence to determine whether mammography is likely to be beneficial in their older women patients (Table 2).

Breast cancer is a heterogeneous disease with considerable variation in its natural history at all ages.[63] However, older women have a greater frequency of cancers with histologies and tumor markers indicative of reduced aggressiveness.[64] For example, low proliferative rates are more common in breast cancers of older women.[65] Therefore, although randomized trials suggest a reduction in mortality from breast cancer that begins to emerge by 4 to 5 years after screening in women aged 50 to 69 years, this lag-time to benefit could be longer for older women.[45] However, treatment of localized breast cancer in older women is associated with less morbidity and better survival than that of advanced disease.[66,67]

In addition, with advancing age the breast's radiographically dense fibroglandular tissue decreases; as a result, the accuracy of mammography for detecting cancers increases.[68] The sensitivity of mammography for detecting cancer is estimated at 73% for women aged 60 to 69 years and 86% for women aged 80 to 89 years.[69] The greater proportion of slow-growing cancers in elderly women contributes to this increased sensitivity.[70] Specificity is estimated at 94% for women aged 70 years or older compared with 91% for women in their 40s, so the risk of false-positive results decreases with advancing age.[53,69] Fewer data are available on the accuracy of clinical breast examination, but 2 series suggest its sensitivity falls after age 50 years.[54,71]

Individual patient characteristics also influence the likelihood of benefit or harm from screening. Advancing age, a family history of breast cancer, a longer duration of estrogen exposure (endogenous or exogenous), and lack of previous mammograms all increase the risk of dying from breast cancer, and thereby increase the chance to benefit from screening.[6,40,62] Conversely, benefit is unlikely among women with serious comorbidity. Several studies have shown that detecting breast cancer at an early stage does not improve the survival of women with multiple comorbid illnesses (Charlson Comorbidity Index $\geq$2).[72,73] In addition, based on the lag-time between screening and survival benefit, older women who have a life expectancy less than 5 years are more likely to be harmed than to benefit from screening.[13,60]

In summary, although advancing age may be associated with a higher proportion of slow-growing breast cancers, older women have a higher absolute risk of dying from breast cancer, and mammography is more accurate in older women. These differing effects make the extrapolation of mammography benefit to older women complex. However, there is no evidence that the benefit of screening ceases at a specific age, so most guidelines recommend screening women over age 70 years. Decisions to stop screening should be based on whether a patient has comorbidities that limit her life expectancy to less than 5 years (Table 3).

Cervical cancer

Evidence of benefit

No prospective trial of screening for cervical cancer has been conducted in any age group. However, multiple observational studies provide good evidence that cytologic screening using Papanicolaou (Pap) smears reduces the incidence and mortality from invasive cervical cancer in women less than 65 years of age.[7,8] In North America and Europe, mortality from cervical cancer declined by 20% to 60% after the introduction of Pap screening programs, which were targeted to women less than 65 years of age.[7] A large number of case-control studies have consistently demonstrated that Pap screening is associated with 60% to 90% reductions in the incidence of invasive cervical cancer, but few studies included older women.[74] Data suggesting screening efficacy increases when Pap smears are performed more frequently also comes from studies of younger women. In a study involving 1.8 million women aged 20 to 64 years, the incidence of invasive cervical cancer was reduced by 64% when the interval between Pap smears was 10 years, by 84% when it was 5 years, by 91% when it was 3 years, and by 93% when it was 1 year.[75]

Evidence of harm

In a cohort study of 2561 postmenopausal women aged 44 to 79 years (mean age, 67 years) with a normal Pap smear, 110 women had an abnormal Pap smear within the next 2 years and all but 1 were false positive.[76] To identify the 1 woman with mild-to-moderate cervical dysplasia, clinicians performed 5019 Pap smears, 33 colposcopies, 8 endometrial biopsies, 35 endocervical curettages, 30 cervical/vaginal biopsies, 4 dilation and curettage procedures, and 9 cone biopsies/loop electrosurgical excision procedures, all of which have attendant risks. An analysis of Medicare claims estimated that 39 of 1000 older women who are screened would require at least 1 follow-up procedure within 8 months.[77]

Pap screening may also cause harm by detecting inconsequential disease. Although cervical cancer typically develops 10 to 30 years after infection with oncogenic types of human papilloma virus, the majority of infections cause only low-grade cervical lesions that regress without treatment.[78,79] Most women undergo treatment when these lesions are detected by screening because of the inability to identify which lesions will progress.[80] Women who undergo treatment for screen-detected lesions that would have regressed naturally have been harmed by screening.

In addition, women who have abnormal Pap smear results frequently report high anxiety, discord with their partner, and low self-esteem.[81,82] This psychological distress may persist even after a normal follow-up examination.

Extrapolating benefits and harms of screening to older patients

There is a paucity of data concerning the benefits of screening for cervical cancer in women over age 70 years. Therefore, clinicians must weigh indirect evidence when deciding whether to extrapolate the benefits of Pap smear screening to older women (Table 2).

Cervical cancer in older women is not more aggressive than in younger women.[83,84] Localized cancer in elderly women also responds well to treatment and is associated with less morbidity and better survival than is advanced disease.[35,85]

However, anatomic changes associated with advancing age may decrease the accuracy of Pap screening. For younger women, the sensitivity of the Pap smear ranges from 30% to 87% and specificity ranges from 86% to 100%.[86] The sensitivity of Pap smears is assumed to be less in older women because the target region for detecting cervical cancer, the squamo-columnar junction, moves higher into the cervical canal, making sampling more difficult.[80,87] Specificity also may be decreased because atrophic changes that occur after menopause increase vulnerability to inflammation, which can mimic neoplasia.[80] More research is needed to determine whether older women have more false-positive results and whether the protective effect of screening is less because Pap smears miss more cancers. In addition, the benefit of testing for human papilloma virus as an adjunct to Pap smear screening has not been evaluated in prospective studies, and evidence regarding its sensitivity and specificity are limited.[83]

Therefore, individual patient characteristics are the driving forces for estimating screening benefit and harm. The main factors that decrease the benefit of Pap screening are a history of normal Pap smears, a limited life expectancy, or having had a hysterectomy.[7-9] Older women who have no evidence of recent cervical abnormalities and have been screened regularly are at extremely low risk for developing cervical cancer (lifetime risk is less than 0.8%), and therefore these women are unlikely to benefit from screening.[88] The vast majority of older women who die of cervical cancer have not been regularly screened.[89] Also, given the long preinvasive phase of cervical dysplasia, older women who have serious comorbidity with a life expectancy less than 5 to 10 years are more likely to suffer harms from screening than to benefit from it.[13] Finally, older women who have undergone total hysterectomy (cervix removed) for a benign indication are not at risk for cervical cancer and should not be screened.[7,88]

In summary, most guidelines recommend that Pap smears be performed in women over age 70 years who have not been regularly screened before. Older women with repeatedly normal Pap smears may stop screening at age 65 or 70 years, as can women at any age who have a short life expectancy or who no longer have a cervix (Table 3).

Conclusions

Decisions about screening for cancer in older persons require weighing potential benefits and harms for each person rather than relying on arbitrary age cutoffs. Given the heterogeneity in life expectancy at older ages, we may find ourselves recommending screening to a healthy, vigorous 90-year-old while discouraging screening in an unhealthy, frail 75-year-old.[90] In addition, because the point at which harms outweigh benefits is subjective, it is important to discuss these issues with older patients and determine whether they would agree to follow-up testing or treatment if required.[13,91] Older patients who would decline follow-up or treatment should not be screened. In addition, for older patients who are bothered by the discomfort and risks of screening tests, the decrease in quality of life in the present may outweigh the small chance of future benefit.[92] By encouraging informed decisions, screening may be more appropriately targeted to older persons for whom the potential benefits outweigh the potential harms.

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