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REVIEW ARTICLE

Impact of Age, Sex, and Comorbidity on Cancer Therapy and Disease Progression

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ABSTRACT

A theme of personalized medicine was highlighted at the 2009 Annual Meeting of the American Society of Clinical Oncology. To this end, the current review focuses on the impact of host characteristics (such as age, sex, and comorbidity) as they pertain to cancer biology, treatment efficacy, and tolerance. Increasing age is associated with complex changes in physiology, including alterations in renal and hepatic function, and decreased bone marrow reserve. These may in turn result in alterations in pharmacokinetics and toxicity related to many commonly used anticancer agents. Using tools, such as the geriatric assessment, may help to elucidate the physiologic age of the patient as opposed to the chronologic age. Increasing age is paralleled by an increase in comorbidity, and comorbidity may have independent prognostic implications and substantially impact medical decision making in the patient with cancer. Numerous biologic ties between cancer and comorbidity exist, one example being an association of diabetes with an increased risk of disease recurrence and mortality in the setting of colon cancer. Biologic features can also vary by sex; several biomarkers with either prognostic or predictive value (ie, excision-repair cross-complementation group 1 expression, epidermal growth factor receptor mutation, or dihydropyrimidine dehydrogenase polymorphism) may differentiate efficacy or toxicity in males and females. Taken together, age, sex, and comorbidity each encompass a complex array of physiologic and molecular variations that may each aid in personalizing care for the patient with cancer.

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INTRODUCTION

The 2009 Annual Meeting of the American Society of Clinical Oncology stressed personalized medicine, a recognition that each patient is unique in "prognosis, treatment tolerance, supportive care needs, and outcomes."[1] An essential part of personalized medicine involves understanding how host characteristics (such as age, comorbidity, or sex) affect cancer biology, treatment efficacy, and tolerance. This is particularly important for potentially vulnerable groups, such as older adults or those with comorbid conditions. The main challenge to personalizing and optimizing their care has been their under-representation in clinical trials, despite the fact that approximately 60% of cancer incidence and 70% of cancer mortality occurs in individuals older than 65 years.[2,3] Furthermore, increasing age is paralleled by an increase in comorbid illnesses.[4] The presence of comorbidity may preclude participation in certain clinical trials, and among those who do enroll, detailed data regarding comorbid conditions is not routinely captured. Finally, although the significance of sex in the treatment of nonsex-specific malignancies (eg, lung and colorectal cancer) has long been recognized in seminal studies, preclinical investigations are just now providing insight into the biology underlying these differences.[5,6]

With the aging of the US and worldwide population and the emergence of personalized medicine, the importance of incorporating patient-related factors into oncology decisions is being recognized. In this article, we review the role of age, sex, and comorbidity in cancer progression and associated therapy, and propose future research that will further aid in the mission of personalized care.

AGE

Cancer is a disease associated with aging—the majority of cancer diagnoses and deaths occur in people older than 65 years—and the United States population is rapidly aging, with a projected doubling in the number of individuals age ≥ 65 from the year 2000 to 2030. On the basis of the aging of the US population and the known association between cancer and aging, a dramatic increase in the number of new cancer diagnoses is projected for the next 20 years (Fig 1). It is anticipated that patients age ≥ 65 will

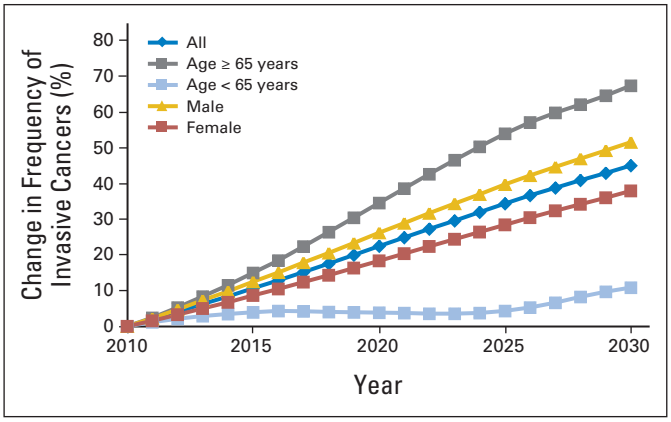

Fig 1. Projected change in frequency of invasive cancers in the United States by age and sex. Nonmelanoma skin cancers were excluded from projections. Data adapted.[7]

account for 70% of all cancer diagnoses by the year 2030.[7] Numerous explanations have been offered as to the biologic connection between cancer and aging, including extended exposure to carcinogens,[8] increased DNA instability resulting in a higher mutation potential,[9] telomere shortening,[10] immune dysregulation,[11] and increased susceptibility to oxidative stress.[12] While these explanations for the link between cancer and aging are plausible, they do not pinpoint the reason why one older adult is more susceptible to cancer than another. Furthermore, the association between cancer and aging is complex. Population-based studies demonstrate a steady rise in the probability of developing cancer across the strata of age,[13] but few studies have examined cancer prevalence and mortality at the extremes of age, and provocative data suggest a potential decrease in cancer prevalence at age ≥ 85.[14,15]

Cancer biology may also differ by age at presentation, and understanding the association between the biology of specific cancers and aging can help guide clinical practice. For example, in the setting of acute myeloid leukemia, an increased incidence of unfavorable cytogenetics and greater antecedent myelodysplasia is observed among older adults.[16] Similarly, in breast cancer, tumor characteristics vary with age. There is an increase in hormone receptor–positive tumors and a decrease in human epidermal growth factor receptor 2 (HER2) overexpression with increasing age.[17] As HER2 and estrogen receptor (ER) status play a critical role in HER2-directed and endocrine therapies, respectively, understanding age-related variations in expression is critical in determining the particular tumor biology and treatment options. An understanding of tumor biology has already led to some distinct algorithms for treating older individuals.[18,19]

The aging process is associated with a decrease in physiologic reserve. This decreased reserve can affect tolerance of anticancer therapy secondary to physiologic changes that occur in multiple organ systems. Decreases in renal blood flow and consequent declines in glomerular filtration with age may affect the clearance of cytotoxic agents that are renally excreted, such as cisplatin, carboplatin, etoposide, and methotrexate.[20-23] A serum creatinine does not accurately reflect renal function in older adults because of the decreasing muscle mass associated with aging. Therefore, a measure of glomerular filtration rate is required to provide a more accurate estimate of renal function with increasing age. Increasing age is also associated with decreased secretion of gastric enzymes and decreased splanchnic blood flow, which may impact the gastrointestinal absorption of orally administered agents, such as capecitabine.[24,25] Liver mass and cytochrome p450 content appear to decline with increasing age, although the clinical impact of these changes is controversial.[26,27] Decreased bone marrow reserve with aging may result in increased toxicity with myelosuppressive therapies in older adults.[20] As a consequence, National Comprehensive Cancer Network and American Society of Clinical Oncology guidelines note age ≥ 65 as a clinical factor for consideration of primary prophylaxis with WBC growth factors.[28,29]

Given the complex physiologic changes that accompany aging, several studies have attempted to characterize alterations in pharmacokinetic parameters and resultant toxicities in older adults (Table 1).[30-41] In turn, these data have prompted efforts to

Table 1. Selected Pharamocokinetic Studies of Single Cytotoxic Agents in Older Adults

Agent	Dosing Regimen	Pharmacokinetic Analysis	Toxicity in Older Adults
Fluorouracil	1,000 mg/m^2 IV continuous infusion days 1-5[30]	Clearance: ⇆ with age; ↓ in female sex	NR
Capecitabine	2,000 mg oral daily[31]	Clearance: ⇆ with age	NR
Docetaxel	40 mg/m^2 IV over 2 hours weekly[32]	Clearance: ⇆ with age	NR
	75 mg/m^2 IV over 1 hour every 3 weeks[33]	Clearance: ⇆	↑ grade 4 neutropenia
Doxorubicin	30-75 mg/m^2 IV[34]	Clearance: ↓ with age	NR
Etoposide	50-75 mg/d[35]	Clearance: ⇆ with age	Grade ≥ 3 neutropenia: ↑ with age
Methotrexate	7.5-15 mg IM weekly[23]	Clearance: ↓ with age; ↑ with ↑ CrCl	NR
Oxaliplatin	130 mg/m^2 IV over 2 hours[36]	Clearance: ⇆ with age; ↑ with ↑ GFR	Toxicity: ⇆ with age
Paclitaxel	175 mg/m^2 IV over 3 hours every 3 weeks[37]	Clearance: ↓	Grade ≥ 3 neutropenia: ↑ with age
	90 mg/m^2 IV over 1 hour weekly for 6 weeks followed by a 2-week break[38]	Clearance: ↓ with age	NR
Temozolomide	100-200 mg/m^2/d oral for 5 days every 28 days[39]	Clearance: ⇆ with age	Neutropenia/thrombocytopenia: ↑ in older females
Vinorelbine	20-30 mg/m^2 IV over 10 minutes weekly[40]	Clearance: ↓ with age	Anemia/neutropenia: ↑ with ↑ AUC
	30 mg/m^2 IV days 1 and 8 every 3 weeks[41]	Clearance: ⇆	Increased neutropenia

NOTE. Changes observed in older adults reflect either comparison to younger historical cohorts or correlations observed with increasing age.
Abbreviations: IV, intravenous; ⇆, no change; ↓, decreased; NR, not reported; ↑, increased; IM, intramuscular; CrCl, creatinine clearance; GFR, glomerular filtration rate; AUC, area under the curve.

Table 2. Components of the CGA and Selected Examples Indicating the Implications of These Subdomains on Cancer Treatment and Prognosis

CGA Component	Implications for Cancer Treatment and Prognosis: Selected Examples
Functional status	Disability in the IADLs are associated with decreased survival in NSCLC and acute leukemia[44,45]
Comorbid (coexisting) medical conditions	Increasing extent of comorbidity has been associated with parallel increases in cancer-specific and all-cause mortality in patients with breast cancer[46]
Cognition	Presence of dementia may decrease the likelihood of receiving adjuvant systemic therapy in breast and colorectal cancer[47,48]
Psychological status	Distress correlates with poorer physical function in patients with solid tumors[49]
Social functioning and support	An increase in all-cause and cancer-specific mortality has been observed in older women with breast cancer who are socially isolated[50]
Socioeconomic issues	Older patients with limited finances may forgo purchase of supportive care medications in favor of purchasing anticancer therapy, thereby decreasing their ability to tolerate treatment[51]
Medication review	Studies of older adults with cancer suggest an average of up to 9 medications per patient, with limited efforts to assess for drug-drug interactions with chemotherapy[52]
Nutritional status	Weight loss prior to initiation of chemotherapy has been linked to poor outcome in multiple tumor types, including colorectal cancer and NSCLC[53,54]

Abbreviations: CGA, Comprehensive Geriatric Assessment; IADL, instrumental activities of daily living; NSCLC, non–small-cell lung cancer.

identify dosing regimens that minimize toxicity but preserve efficacy in older patients.[42]

Aging is a heterogeneous process. Evaluation tools, such as the comprehensive geriatric assessment, allow for identification of older patients with a higher risk of morbidity and mortality. In these individuals, the risks and benefits of anticancer therapy must be specifically assessed.[43] The geriatric assessment includes domains with prognostic relevance that afford insight into the physiologic age of the patient, as opposed to the chronologic age alone (Table 2).[44-54] Evaluation with a geriatric assessment is being studied by the Cancer and Leukemia Group B (ClinicalTrials.gov Identifier: NCT00416481).[55]

A clinical phenotype to risk-stratify an older patient population for frailty has been reported in the geriatric literature and is of enormous prognostic value. This phenotype is characterized by five features: self-reported exhaustion, weakness (by grip strength), unintentional weight loss (greater than 10 pounds in the past year), slow walking speed, and low physical activity.[56] Patients with ≥ three or more of these criteria (thereby characterized as frail) have a significantly higher risk of both hospitalization and death as compared with nonfrail individuals. This prognostic phenotype has been validated in several large data sets.[57,58] Further research is needed to explore the application of these criteria to older adults with cancer.

COMORBIDITY

With increasing age, the number of comorbid illnesses increases. In a study of 7,600 patients older than 55 years with cancer, those age 55 to 64 had an average of 2.9 comorbid conditions compared with patients age ≥ 75, who had an average of 4.2 comorbid conditions.[59] Comorbidity has important prognostic implications. An observational cohort study including 17,712 patients receiving care for multiple cancer types suggested that the severity of comorbidities affected overall survival (OS) in a dose-dependent fashion, independent of cancer stage.[4] When formulating a treatment plan, oncologists juxtapose the risk from the malignancy against that of comorbid illness on life expectancy. The effect of treatment in decreasing this risk is also weighed. Utilizing this framework, indolent cancers may be managed more conservatively in the setting of a substantial comorbid disease that is more likely to have an impact on life expectancy. In contrast, more aggressive malignancies warrant cancer therapy if they are more likely to affect life expectancy than the comorbid illness.

In practice, it appears that weighing risks of comorbidity does take place, albeit in the absence of firm guidelines. The presence and extent of comorbidity appears to impact surgical decision making in oncology, such as the use of axillary dissection, radical prostatectomy, and resection for breast, prostate, and lung cancer, respectively.[60-62] Similarly, comorbidity appears to affect utilization of chemotherapy across multiple malignancies.[63-65] It is possible that the latter trend reflects studies suggesting greater chemotherapy-related toxicity among patients with comorbidity,[66,67] although conflicting data does exist.[68]

Specific comorbidities may have a unique bearing on prognosis and treatment outcome. In a series of 5,077 patients treated with neoadjuvant hormone therapy followed by radiation for localized prostate cancer, use of hormone therapy was associated with a higher risk of all-cause mortality in the presence of coronary artery disease, congestive heart failure (CHF), or prior myocardial infarction (26.3% *v* 11.2%; $P = .04$).[69] In contrast, no increased risk of mortality was observed in men without comorbidity or with only one coronary artery disease risk factor. Other studies have investigated the role of diabetes in the progression of malignancy. Subset analyses of Intergroup-0089 (INT-0089), a randomized trial comparing four fluorouracil-based adjuvant therapy regimens in patients with stage II and III colon cancer, supported several smaller studies that identified a higher rate of overall mortality in patients with colon cancer who also had diabetes.[70-72] Molecular rationale for this phenomenon may be linked to elevated serum levels of insulin, which accelerates proliferation of colorectal cell lines.[73] Providing clinical validation for this theory, a study of surgically resected patients with colorectal cancer reported that higher levels of C peptide and low levels of insulin-like growth factor binding protein-1 were associated with increased mortality.[74] Similar findings have been noted in patients with breast cancer, where elevated fasting insulin levels have been associated with an increased risk of distant recurrence and mortality in early-stage disease.[75] These studies have led to the development of clinical trials evaluating whether modulating the insulin axis would affect cancer outcomes. A provocative study assessing patients from the M. D. Anderson Cancer Registry identified a higher rate of pathologic complete response with neoadjuvant chemotherapy among diabetic patients taking metformin as compared with nondiabetic patients.[76] These and other supporting data have led to the development of a phase III intergroup trial (National Cancer Institute of Canada MA.32) examining the effect of metformin as adjuvant therapy for breast cancer.[77] The evolving understanding of the relationship between breast cancer and diabetes, ultimately leading to a potential

therapeutic intervention, underscores the importance of understanding the link between comorbidity and cancer.

It is increasingly recognized that comorbidity may also have a substantial impact on treatment tolerance. In the setting of advanced lung cancer, a randomized trial comparing vinorelbine alone or in combination with gemcitabine demonstrated a higher rate of treatment discontinuation among patients with a Charlson comorbidity index (CCI) score of higher than 2.[78] Supporting this finding, data from a series of patients with breast cancer receiving dose-dense adjuvant chemotherapy identified an association between comorbidity (defined as a CCI ≥ 1) and grade 3/4 toxicity.[79] Certain comorbidities may have an impact on tolerance for specific therapies as well. For instance, early observations with paclitaxel therapy suggested an increased risk for severe neuropathy in patients with a concomitant diagnosis of diabetes.[80] Similarly, the risk of cardiac toxicity with the HER2-directed monoclonal antibody trastuzumab is higher in patients with pre-existing hypertension.[81,82]

Of note, an effort should be made to distinguish comorbidity from treatment-related toxicity, as these may have different prognostic implications. As one example, the vascular endothelial growth factor targeting antibody bevacizumab has been noted to cause hypertension in clinical application across malignancies.[83-85] Subset analyses from pivotal trials of bevacizumab in lung and breast cancer have associated the development of hypertension with extended OS.[86,87] These results have led some investigators to question whether hypertension should be considered a dose-limiting toxicity.[88]

SEX

The approach to diseases such as prostate and breast cancer has been guided by an understanding of distinct hormonal axes in males and females, respectively. In other malignancies more evenly distributed between the sexes, key differences in biology between men and women are increasingly recognized. These differences often lead to variations in therapeutic response, toxicity, and clinical outcome. For instance, in the early 1990s, female sex was identified as an independent predictor of survival in patients with lung cancer.[89] It has been surmised that molecular variations may account for this difference. As one example, excision-repair cross-complementation group 1 (ERCC1), a DNA repair protein, has previously been validated as a predictor of survival with platinum-based therapy for non–small-cell lung cancer (NSCLC) in the adjuvant and metastatic setting.[90-92] In patients with inoperable NSCLC, receiving first-line therapy with cisplatin and gemcitabine and lack of ERCC1 expression characterized a subset of males with poorer OS (7.9 *v* 11.8 months; $P = .005$).[93] In contrast, OS was no different in females with ERCC1–negative or –positive tumors (12.6 *v* 12.3 months; $P = .70$). Other molecular aberrations may predict differences in response to novel targeted therapies for NSCLC. A phase III trial of the epidermal growth factor receptor (EGFR) inhibitor erlotinib demonstrated improved survival with the agent (compared with placebo) after first- or second-line therapy.[94] The study further identified enhanced response rates among females and those with *EGFR* mutation, a finding supported by several other investigations of erlotinib and the related EGFR inhibitor gefitinib.[94-98] Higher rates of *EGFR* mutation have been found in female patients with NSCLC, perhaps accounting in part for the discrepancy in response rates by sex.[99]

Aside from differences in clinical outcome, men and women may differ in the extent to which they experience toxicity from chemotherapy and biologics. A meta-analysis including 1,006 patients with small-cell lung cancer enrolled in one of four National Cancer Institute of Canada chemotherapy protocols demonstrated more frequent hematologic toxicity (grade 3 or 4) and gastrointestinal toxicity (all grades) in women.[100] Interestingly, females were noted to have improved response rates and OS with the regimens that included etoposide and cisplatin and cyclophosphamide, doxorubicin, and vincristine.

Other studies have suggested that molecular variations may account for differences in toxicity by sex—as one example, polymorphisms in dihydropyrimidine dehydrogenase (*DYPD*) have been noted to predict grade 3 and 4 toxicity from fluorouracil-based therapy for colorectal cancer.[101] In the same study, a strong association between sex and *DYPD* polymorphism has been observed—while the odds ratio for toxicity in males with *DYPD* polymorphism is 41.3 (95% CI, 9.2 to 190; $P < .001$), the odds ratio for females with the same polymorphism is 1.33 (95% CI, 0.34 to 5.2; $P = .68$). Whereas this study and others have reported a higher rate of toxicity from fluorouracil-based therapy in women (possibly due to increased *DYPD* deficiency),[102,103] it appears that this finding was independent on *DYPD* genotype. Globally, variations in hepatic p-glycoprotein levels (approximately two-fold higher in males than females) may prolong the half-life of various agents, including vinca alkaloids, doxorubicin, etoposide, and docetaxel.[104,105] Decreased levels of this drug efflux protein may lead to accumulation of these agents and consequent toxicity.[106,107]

Mounting evidence suggests that the hormonal axes differentiating men and women could play a role in the pathogenesis and progression of other malignancies outside of male genitourinary and gynecologic cancers. For example, in a series of 228 patients with operable NSCLC, 106 patients (46.5%) demonstrated progesterone receptor (PR) immunoreactivity.[108] Positive staining for PR was associated with lower TNM stage, increased histologic differentiation, and improved OS. Accompanying in vitro studies suggested an inhibitory effect of progesterone in PR-positive NSCLC cell lines, suggesting a potential therapeutic role for hormone therapy. ER may also play a prognostic role in NSCLC. Specimens from a series of 447 patients with lung adenocarcinoma revealed nuclear expression of ER-β in 217 patients (48.5%).[109] Interestingly, the prognostic role of nuclear ER-β was limited to patients with concomitant *EGFR* mutation, where expression was related to improved disease-free survival.

LINKING AGE, SEX, AND COMORBIDITY

While the data presented thus far provide evidence for the separate predictive capabilities of age, sex, and comorbidity in patients with cancer, there are many associations among these variables. Currently, several other prognostic indices for older adults incorporate age, sex, and/or comorbidity (Table 3).[110-113] For example, Lee et al[112] developed a model for 4-year mortality in the general geriatric population which includes age, sex, and comorbidity. Other indices include two of the three variables. For instance, the CCI has been applied to determine the risk of mortality associated with increasing levels of comorbidity (including cancer).[114] In external

Table 3. Indices Utilizing Age, Sex, and/or Comorbidity to Predict Risk of Mortality for Older Adults

Reference	No.	Domains Incorporated			Predictive Capability
		Age	Sex	Comorbidity	
Charlson et al[110]	218	Yes	No	Yes	5-year mortality
Inouye et al[111]	318	No	No	Yes	2-year mortality
Lee et al[112]	8,009	Yes	Yes	Yes	4-year mortality
Walter et al[113]	1,427	No	Yes	Yes	1-year mortality

validation of the CCI, it was demonstrated that consideration of age as an adjunct to the CCI could improve the predictive capability of the tool.[110] Studies in the geriatric oncology population have also demonstrated the importance of these variables. In the setting of colorectal carcinoma, a model developed through a Surveillance, Epidemiology, and End Results registry review utilized the three variables in addition to disease stage to predict early mortality.[72] Other studies demonstrate a link between comorbidity and clinical outcome among older adults with cancer. A Surveillance, Epidemiology, and End Results-Medicare analysis of 29,733 patients with stage I to III colorectal cancer age 67 or older suggested that a substantial proportion of deaths in this population could be attributed to concomitant diagnoses of diabetes mellitus, chronic obstructive pulmonary disease, and/or CHF.[115] In the setting of hematologic malignancies, a series of 1,708 patients age 66 or older with myelodysplastic syndrome identified the CCI as a significant predictor of mortality; specifically, patients with CHF and/or chronic obstructive pulmonary disease had significantly shorter survival.[116] The link between age, comorbidity, and clinical outcome has been made in the setting of multiple other malignancies, including prostate, lung, and ovarian cancer.[117-119]

More specific molecular variations may differ with age and sex. The tumor suppressor $p16^{INK4a}$ has been noted to be a potential marker of physiologic age because with aging, $p16^{INK4a}$ expression increases in the tissues of both humans and rodents.[120] Aberrant methylation of the tumor suppressor gene $p16^{INK4a}$ is seen primarily in females and patients of advanced age, a finding seen in both colorectal cancer and hepatocellular carcinoma.[121,122] In colorectal cancer, hypermethylation of $p16^{INK4a}$ appeared to occur in poorly differentiated tumors. As another example of age and sex associations with a distinct genotype, the SNP309 polymorphism in *MDM2* (a negative regulator of p53), which has been associated with melanoma in women younger than 50 years.[123] As similar molecular markers are identified in the future, therapeutic strategies may emerge based on specific demographic criteria.

SUMMARY

Reflecting on the theme of personalized medicine, the data described here provide a framework in which to consider age, sex, and comorbidity in cancer biology and treatment. Each element portends distinct prognostic value, and is associated with both shared and unique molecular attributes.

Despite the progress being made in understanding the implications of these variables, challenges remain. While age follows a continuum and sex can be represented as a dichotomous variable, comorbidity is more challenging to characterize. In response, the National Institute on Aging Geriatrics and Gerontology program has assembled a taskforce to specifically address the construction of comorbidity measures, proposing standardized schema such as the staging algorithms employed in cancer.[124]

A separate but important barrier related to older adults and patients with comorbidities is their under-representation in clinical trials.[2] In addition to inclusion in standard protocols, trials that address age-specific needs in older adults may also yield vital insights.[125] To promote enrollment of older adults in trials, it may be necessary to relax the eligibility criteria by focusing on developing therapeutics in patients with comorbid illnesses, with particular attention to the association between comorbidity and treatment tolerance.[126]

Given the advancing age of US society and the world at large, clinical trials focused on optimizing cancer therapeutics for both fit and frail older adults are urgently needed.

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REFERENCES

1. Schilsky RL: Personalizing cancer care: American Society of Clinical Oncology presidential address 2009. J Clin Oncol 27:3725-3730, 2009

2. Hutchins L, Unger J, Crowley J, et al: Underrepresentation of patients 65 years of age or older in cancer-treatment trials. N Engl J Med 341:2061-2067, 1999

3. Ries LAG, Melbert D, Krapcho M, et al: SEER cancerstatisticsreview,1975-2005.http://seer.cancer.gov/statfacts/html/all.html

4. Piccirillo JF, Tierney RM, Costas I, et al: Prognostic importance of comorbidity in a hospital-based cancer registry. JAMA 291:2441-2447, 2004

5. Wakelee HA, Wang W, Schiller JH, et al: Survival differences by sex for patients with advanced non-small cell lung cancer on Eastern Cooperative Oncology Group trial 1594. J Thorac Oncol 1:441-446, 2006

6. Giacchetti S, Bjarnason G, Garufi C, et al: Phase III trial comparing 4-day chronomodulated therapy versus 2-day conventional delivery of fluorouracil, leucovorin, and oxaliplatin as first-line chemotherapy of metastatic colorectal cancer: The European Organisation for Research and Treatment of Cancer Chronotherapy Group. J Clin Oncol 24:3562-3569, 2006

7. Smith BD, Smith GL, Hurria A, et al: Future of cancer incidence in the United States: Burdens upon an aging, changing nation. J Clin Oncol 27: 2758-2765, 2009

8. Kaiser JC, Heidenreich WF, Monchaux G, et al: Lung tumour risk in radon-exposed rats from different experiments: Comparative analysis with biologically based models. Radiat Environ Biophys 43:189-201, 2004

9. Slebos RJC, Li M, Vadivelu S, et al: Microsatellite mutations in buccal cells are associated with aging and head and neck carcinoma. Br J Cancer 98:619-626, 2008

10. Campisi J, Kim S-h, Lim C-S, et al: Cellular senescence, cancer and aging: The telomere connection. Exp Gerontol 36:1619-1637, 2001

11. Lustgarten J: Cancer, aging and immunotherapy: Lessons learned from animal models. Cancer Immunol Immunother 58:1979-1989, 2009

12. Song YS, Lee BY, Hwang ES: Dinstinct ROS and biochemical profiles in cells undergoing DNA damage-induced senescence and apoptosis. Mech Ageing Dev 126:580-590, 2005

13. Jemal A, Center MM, Ward E, et al: Cancer occurrence, in Verma M (ed): Cancer Epidemiology (vol 1). New York, NY, Humana Press, 2009, pp 3-29

14. Kanapuru B, Posani K, Muller D, et al: Decreased cancer prevalence in the nursing home. J Am Geriatr Soc 56:2165-2166, 2008

15. Stanta G, Campagner L, Cavallieri F, et al: Cancer of the oldest old: What we have learned from autopsy studies. Clin Geriatr Med 13:55-68, 1997

16. Appelbaum FR, Gundacker H, Head DR, et al: Age and acute myeloid leukemia. Blood 107: 3481-3485, 2006

17. Diab SG, Elledge RM, Clark GM: Tumor characteristics and clinical outcome of elderly women with breast cancer. J Natl Cancer Inst 92:550-556, 2000

18. Kantarjian H, O'Brien S, Cortes J, et al: Results of intensive chemotherapy in 998 patients age 65 years or older with acute myeloid leukemia or high-risk myelodysplastic syndrome. Cancer 106: 1090-1098, 2006

19. Lowenberg B, Ossenkoppele GJ, van Putten W, et al: High-dose daunorubicin in older patients with acute myeloid leukemia. N Engl J Med 361: 1235-1248, 2009

20. Vestal RE: Aging and pharmacology. Cancer 80:1302-1310, 1997

21. Go RS, Adjei AA: Review of the comparative pharmacology and clinical activity of cisplatin and carboplatin. J Clin Oncol 17:409-422, 1999

22. Toffoli G, Corona G, Sorio R, et al: Population pharmacokinetics and pharmacodynamics of oral etoposide. Br J Clin Pharmacol 52:511-519, 2001

23. Bressolle F, Bologna C, Kinowski JM, et al: Effects of moderate renal insufficiency on pharmacokinetics of methotrexate in rheumatoid arthritis patients. Ann Rheum Dis 57:110-113, 1998

24. Baker SD, Grochow LB: Pharmacology of cancer chemotherapy in the older person. Clin Geriatr Med 13:169-183, 1997

25. Yuen GJ: Altered pharmacokinetics in the elderly. Clin Geriatr Med 6:257-267, 1990

26. Sotaniemi EA, Arranto AJ, Pelkonen O, et al: Age and cytochrome P450-linked drug metabolism in humans: An analysis of 226 subjects with equal histopathologic conditions. Clin Pharmacol Ther 61: 331-339, 1997

27. Sawhney R, Sehl M, Naeim A: Physiologic aspects of aging: Impact on cancer management and decision making, part I. Cancer J 11:449-460, 2005

28. NCCN Practice Guidelines in Oncology (v. 1.2009): Myeloid growth factors. http://www.nccn.org/professionals/physician_gls/PDF/myeloid_growth.pdf

29. Smith TJ, Khatcheressian J, Lyman GH, et al: 2006 Update of recommendations for the use of white blood cell growth factors: An evidence-based clinical practice guideline. J Clin Oncol 24:3187-3205, 2006

30. Milano G, Etienne M, Cassuto-Viguier E, et al: Influence of sex and age on fluorouracil clearance. J Clin Oncol 10:1171-1175, 1992

31. Cassidy J, Twelves C, Cameron D, et al: Bioequivalence of two tablet formulations of capecitabine and exploration of age, gender, body surface area, and creatinine clearance as factors influencing systemic exposure in cancer patients. Cancer Chemother Pharmacol 44:453-460, 1999

32. Slaviero KA, Clarke SJ, McLachlan AJ, et al: Population pharmacokinetics of weekly docetaxel in patients with advanced cancer. Br J Clin Pharmacol 57:44-53, 2004

33. ten Tije AJ, Verweij J, Carducci MA, et al: Prospective evaluation of the pharmacokinetics and toxicity profile of docetaxel in the elderly. J Clin Oncol 23:1070-1077, 2005

34. Li J, Gwilt PR: The effect of age on the early disposition of doxorubicin. Cancer Chemother Pharmacol 51:395-402, 2003

35. Ando M, Minami H, Ando Y, et al: Pharmacological analysis of etoposide in elderly patients with lung cancer. Clin Cancer Res 5:1690-1695, 1999

36. Graham MA, Lockwood GF, Greenslade D, et al: Clinical pharmacokinetics of oxaliplatin: A critical review. Clin Cancer Res 6:1205-1218, 2000

37. Lichtman S, Hollis D, Miller A, et al: Prospective evaluation of the relationship of patient age and paclitaxel clinical pharmacology: Cancer and Leukemia Group B (CALGB 9762). J Clin Oncol 24:1846-1851, 2006

38. Fidias P, Supko JG, Martins R, et al: A phase II study of weekly paclitaxel in elderly patients with advanced non-small cell lung cancer. Clin Cancer Res 7:3942-3949, 2001

39. Jen JF, Cutler DL, Pai SM, et al: Population pharmacokinetics of temozolomide in cancer patients. Pharm Res 17:1284-1289, 2000

40. Gauvin A, Pinguet F, Culine S, et al: Bayesian estimate of vinorelbine pharmacokinetic parameters in elderly patients with advanced metastatic cancer. Clin Cancer Res 6:2690-2695, 2000

41. Sorio R, Robieux I, Galligioni E, et al: Pharmacokinetics and tolerance of vinorelbine in elderly patients with metastatic breast cancer. Eur J Cancer 33:301-303, 1997

42. Bajetta E, Procopio G, Celio L, et al: Safety and efficacy of two different doses of capecitabine in the treatment of advanced breast cancer in older women. J Clin Oncol 23:2155-2161, 2005

43. Klepin H, Mohile S, Hurria A: Geriatric assessment in older patients with breast cancer. J Natl Compr Canc Netw 7:226-236, 2009

44. Maione P, Perrone F, Gallo C, et al: Pretreatment quality of life and functional status assessment significantly predict survival of elderly patients with advanced non-small-cell lung cancer receiving chemotherapy: A prognostic analysis of the multicenter Italian lung cancer in the elderly study. J Clin Oncol 23:6865-6872, 2005

45. Wedding U, Röhrig B, Klippstein A, et al: Age, severe comorbidity and functional impairment independently contribute to poor survival in cancer patients. J Cancer Res Clin Oncol 133:945-950, 2007

46. Satariano WA, Ragland DR: The effect of comorbidity on 3-year survival of women with primary breast cancer. Ann Intern Med 120:104-110, 1994

47. Gupta SK, Lamont EB: Patterns of presentation, diagnosis, and treatment in older patients with colon cancer and comorbid dementia. Journal of the American Geriatrics Society 52:1681-1687, 2004

48. Heck JE, Albert SM, Franco R, et al: Patterns of dementia diagnosis in surveillance, epidemiology, and end results breast cancer survivors who use chemotherapy. J Am Geriatr Soc 56:1687-1692, 2008

49. Hurria A, Li D, Hansen K, et al: Distress in older patients with cancer. J Clin Oncol 27:4346-4351, 2009

50. Kroenke CH, Kubzansky LD, Schernhammer ES, et al: Social networks, social support, and survival after breast cancer diagnosis. J Clin Oncol 24:1105-1111, 2006

51. Bried EM, Scheffler RM: The financial stages of cancer in the elderly. Oncology (Williston Park) 6:153-160, 1992

52. Sokol KC, Knudsen JF, Li MM: Polypharmacy in older oncology patients and the need for an interdisciplinary approach to side-effect management. J Clin Pharm Ther 32:169-175, 2007

53. Andreyev HJN, Norman AR, Oates J, et al: Why do patients with weight loss have a worse outcome when undergoing chemotherapy for gastrointestinal malignancies? Eur J Cancer 34:503-509, 1998

54. Buccheri G, Ferrigno D: Importance of weight loss definition in the prognostic evaluation of non-small-cell lung cancer. Lung Cancer 34:433-440, 2001

55. Cohen HJ, Muss HB: The Cancer and Leukemia Group B Cancer in the Elderly Committee: Addressing a major cancer need. Clin Cancer Res 12:3606s-3611s, 2006

56. Fried LP, Tangen CM, Walston J, et al: Frailty in older adults: Evidence for a phenotype. J Gerontol A Biol Sci Med Sci 56:M146-157, 2001

57. Bandeen-Roche K, Xue Q-L, Ferrucci L, et al: Phenotype of frailty: Characterization in the women's health and aging studies. J Gerontol A Biol Sci Med Sci 61:262-266, 2006

58. Xue Q-L, Bandeen-Roche K, Varadhan R, et al: Initial manifestations of frailty criteria and the development of frailty phenotype in the Women's Health and Aging Study II. J Gerontol A Biol Sci Med Sci 63:984-990, 2008

59. Yancik R: Cancer burden in the aged: An epidemiologic and demographic overview. Cancer 80:1273-1283, 1997

60. Konety BR, Cowan JE, Carroll PR: Patterns of primary and secondary therapy for prostate cancer in elderly men: Analysis of data from CaPSURE. J Urol 179:1797-1803, 2008

61. Smith TJ, Penberthy L, Desch CE, et al: Differences in initial treatment patterns and outcomes of lung cancer in the elderly. Lung Cancer 13:235-252, 1995

62. Yancik R, Wesley MN, Ries LAG, et al: Effect of age and comorbidity in postmenopausal breast cancer patients aged 55 years and older. JAMA 285:885-892, 2001

63. Keating NL, Landrum MB, Klabunde CN, et al: Adjuvant chemotherapy for stage III colon cancer: Do physicians agree about the importance of patient age and comorbidity? J Clin Oncol 26:2532-2537, 2008

64. Hurria A, Wong FL, Villaluna D, et al: Role of age and health in treatment recommendations for older adults with breast cancer: The perspective of oncologists and primary care providers. J Clin Oncol 26:5386-5392, 2008

65. Blanco JAG, Toste IS, Alvarez RF, et al: Age, comorbidity, treatment decision and prognosis in lung cancer. Age Ageing 37:715-718, 2008

66. Aparicio T, Desrame J, Lecomte T, et al: Oxaliplatin- or irinotecan-based chemotherapy for metastatic colorectal cancer in the elderly. Br J Cancer 89:1439-1444

67. Asmis TR, Ding K, Seymour L, et al: Age and comorbidity as independent prognostic factors in the treatment of non-small-cell lung cancer: A review of National Cancer Institute of Canada Clinical Trials Group trials. J Clin Oncol 26:54-59, 2008

68. Moscetti L, Nelli F, Padalino D, et al: Gemcitabine and cisplatin in the treatment of elderly patients with advanced non-small cell lung cancer: Impact of comorbidities on safety and efficacy outcome. J Chemother 17:685-692, 2005

69. Nanda A, Chen M-H, Braccioforte MH, et al: Hormonal therapy use for prostate cancer and mortality in men with coronary artery disease-induced congestive heart failure or myocardial infarction. JAMA 302:866-873, 2009

70. Meyerhardt JA, Catalano PJ, Haller DG, et al: Impact of diabetes mellitus on outcomes in patients with colon cancer. J Clin Oncol 21:433-440, 2003

71. Payne JE, Meyer HJ: The influence of other diseases upon the outcome of colorectal cancer patients. Aust N Z J Surg 65:398-402, 1995

72. Yancik R, Wesley MN, Ries LAG, et al: Comorbidity and age as predictors of risk for early mortality of male and female colon carcinoma patients. Cancer 82:2123-2134, 1998

73. Tran TT, Medline A, Bruce WR: Insulin promotion of colon tumors in rats. Cancer Epidemiol Biomarkers Prev 5:1013-1015, 1996

74. Wolpin BM, Meyerhardt JA, Chan AT, et al: Insulin, the insulin-like growth factor axis, and mortality in patients with nonmetastatic colorectal cancer. J Clin Oncol 27:176-185, 2009

75. Goodwin PJ, Ennis M, Pritchard KI, et al: Fasting insulin and outcome in early-stage breast cancer: Results of a prospective cohort study. J Clin Oncol 20:42-51, 2002

76. Jiralerspong S, Palla SL, Giordano SH, et al: Metformin and pathologic complete responses to neoadjuvant chemotherapy in diabetic patients with breast cancer. J Clin Oncol 27:3297-3302, 2009

77. Goodwin PJ, Ligibel JA, Stambolic V: Metformin in breast cancer: Time for action. J Clin Oncol 27:3271-3273, 2009

78. Frasci G, Lorusso V, Panza N, et al: Gemcitabine plus vinorelbine versus vinorelbine alone in elderly patients with advanced non-small-cell lung cancer. J Clin Oncol 18:2529-2536, 2000

79. Zauderer M, Patil S, Hurria A: Feasibility and toxicity of dose-dense adjuvant chemotherapy in older women with breast cancer. Breast Cancer Res Treat 117:205-210, 2008

80. Rowinsky EK, Eisenhauer EA, Chaudhry V, et al: Clinical toxicities encountered with paclitaxel (Taxol). Semin Oncol 20:1-15, 1993

81. Perez EA, Suman VJ, Davidson NE, et al: Cardiac safety analysis of doxorubicin and cyclophosphamide followed by paclitaxel with or without trastuzumab in the North Central Cancer Treatment Group N9831 adjuvant breast cancer trial. J Clin Oncol 26:1231-1238, 2008

82. Suter TM, Procter M, van Veldhuisen DJ, et al: Trastuzumab-associated cardiac adverse effects in the herceptin adjuvant trial. J Clin Oncol 25:3859-3865, 2007

83. Hurwitz H, Fehrenbacher L, Novotny W, et al: Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. N Engl J Med 350:2335-2342, 2004

84. Miller K, Wang M, Gralow J, et al: Paclitaxel plus bevacizumab versus paclitaxel alone for metastatic breast cancer. N Engl J Med 357:2666-2676, 2007

85. Sandler A, Gray R, Perry MC, et al: Paclitaxel-carboplatin alone or with bevacizumab for non-small-cell lung cancer. N Engl J Med 355:2542-2550, 2006

86. Dahlberg SE, Sandler AB, Brahmer JR, et al: Clinical course of advanced non-small cell lung cancer (NSCLC) patients (pts) experiencing hypertension (HTN) during treatment (TX) with bevacizumab (B) in combination with carboplatin (C) and paclitaxel (P) on E4599. J Clin Oncol 27:417s, 2009 (abstr 8042)

87. Schneider BP, Wang M, Radovich M, et al: Association of vascular endothelial growth factor and vascular endothelial growth factor receptor-2 genetic polymorphisms with outcome in a trial of paclitaxel compared with paclitaxel plus bevacizumab in advanced breast cancer: ECOG 2100. J Clin Oncol 26:4672-4678, 2008

88. Jain RK, Duda DG, Sorensen AG: Emerging Paradigms and Potential Biomarkers of Response and Resistance in Antiangiogenic Therapy of Cancer. Alexandria, VA, American Society of Clinical Oncology, 2009, pp 716-721

89. Ferguson M, Skosey C, Hoffman P, et al: Sex-associated differences in presentation and survival in patients with lung cancer. J Clin Oncol 8:1402-1407, 1990

90. Olaussen KA, Dunant A, Fouret P, et al: DNA repair by ERCC1 in non-small-cell lung cancer and cisplatin-based adjuvant chemotherapy. N Engl J Med 355:983-991, 2006

91. Lord RV, Brabender J, Gandara D, et al: Low ERCC1 expression correlates with prolonged survival after cisplatin plus gemcitabine chemotherapy in non-small cell lung cancer. Clin Cancer Res 8:2286-2291, 2002

92. Ceppi P, Volante M, Novello S, et al: ERCC1 and RRM1 gene expressions but not EGFR are predictive of shorter survival in advanced non-small-cell lung cancer treated with cisplatin and gemcitabine. Ann Oncol 17:1818-1825, 2006

93. Holm B, Mellemgaard A, Skov T, et al: Different impact of excision repair cross-complementation group 1 on survival in male and female patients with inoperable non-small-cell lung cancer treated with carboplatin and gemcitabine. J Clin Oncol 27:4254-4259, 2009

94. Shepherd FA, Rodrigues Pereira J, Ciuleanu T, et al: Erlotinib in previously treated non-small-cell lung cancer. N Engl J Med 353:123-132, 2005

95. Lynch TJ, Bell DW, Sordella R, et al: Activating mutations in the epidermal growth factor receptor underlying responsiveness of non-small-cell lung cancer to gefitinib. N Engl J Med 350:2129-2139, 2004

96. Pao W, Miller V, Zakowski M, et al: EGF receptor gene mutations are common in lung cancers from "never smokers" and are associated with sensitivity of tumors to gefitinib and erlotinib. Proc Natl Acad Sci U S A 101:13306-13311, 2004

97. Cappuzzo F, Hirsch FR, Rossi E, et al: Epidermal growth factor receptor gene and protein and gefitinib sensitivity in non-small-cell lung cancer. J Natl Cancer Inst 97:643-655, 2005

98. Han S-W, Kim T-Y, Hwang PG, et al: Predictive and prognostic impact of epidermal growth factor receptor mutation in non-small-cell lung cancer patients treated with gefitinib. J Clin Oncol 23:2493-2501, 2005

99. Tam IY, Chung LP, Suen WS, et al: Distinct epidermal growth factor receptor and KRAS mutation patterns in non-small cell lung cancer patients with different tobacco exposure and clinicopathologic features. Clin Cancer Res 12:1647-1653, 2006

100. Singh S, Parulekar W, Murray N, et al: Influence of sex on toxicity and treatment outcome in small-cell lung cancer. J Clin Oncol 23:850-856, 2005

101. Schwab M, Zanger UM, Marx C, et al: Role of genetic and nongenetic factors for fluorouracil treatment-related severe toxicity: A prospective clinical trial by the German 5-FU Toxicity Study Group. J Clin Oncol 26:2131-2138, 2008

102. Sloan JA, Goldberg RM, Sargent DJ, et al: Women experience greater toxicity with fluorouracil-based chemotherapy for colorectal cancer. J Clin Oncol 20:1491-1498, 2002

103. Milano G, Etienne MC, Pierrefite V, et al: Dihydropyrimidine dehydrogenase deficiency and fluorouracil-related toxicity. Br J Cancer 79:627-630, 1999

104. Benet LZ, Cummins CL, Wu CY: Unmasking the dynamic interplay between efflux transporters and metabolic enzymes. Int J Pharm 277:3-9, 2004

105. Schuetz E, Furuya K, Schuetz J: Interindividual variation in expression of P-glycoprotein in normal human liver and secondary hepatic neoplasms. J Pharmacol Exp Ther 275:1011-1018, 1995

106. Asperen Jv, Tellingen Ov, Tijssen F, et al: Increased accumulation of doxorubicin and doxorubicinol in cardiac tissue of mice lacking mdr1a P-glycoprotein. Br J Cancer 79:108-113, 1998

107. Cummins CL, Wu C-Y, Benet LZ: Sex-related differences in the clearance of cytochrome P450 3A4 substrates may be caused by P-glycoprotein. Clin Pharmacol Ther 72:474-489, 2002

108. Ishibashi H, Suzuki T, Suzuki S, et al: Progesterone receptor in non-small cell lung cancer: A potent prognostic factor and possible target for endocrine therapy. Cancer Res 65:6450-6458, 2005

109. Nose N, Sugio K, Oyama T, et al: Association between estrogen receptor-{beta} expression and epidermal growth factor receptor mutation in the postoperative prognosis of adenocarcinoma of the lung. J Clin Oncol 27:411-417, 2009

110. Charlson M, Szatrowski TP, Peterson J, et al: Validation of a combined comorbidity index. J Clin Epidemiol 47:1245-1251, 1994

111. Inouye SK, Peduzzi PN, Robison JT, et al: Importance of functional measures in predicting mortality among older hospitalized patients. JAMA 279:1187-1193, 1998

112. Lee SJ, Lindquist K, Segal MR, et al: Development and validation of a prognostic index for 4-year mortality in older adults. JAMA 295:801-808, 2006

113. Walter LC, Brand RJ, Counsell SR, et al: Development and validation of a prognostic index for 1-year mortality in older adults after hospitalization. JAMA 285:2987-2994, 2001

114. Charlson ME, Pompei P, Ales KL, et al: A new method of classifying prognostic comorbidity in longitudinal studies: Development and validation. J Chronic Dis 40:373-383, 1987

115. Gross CP, Guo Z, McAvay GJ, et al: Multimorbidity and survival in older persons with colorectal cancer. J Am Geriatr Soc 54:1898-1904, 2006

116. Wang R, Gross CP, Halene S, et al: Comorbidities and survival in a large cohort of patients with newly diagnosed myelodysplastic syndromes. Leuk Res 33:1594-1598, 2009

117. de Cos JS, Miravet L, Abal J, et al: Lung cancer survival in Spain and prognostic factors: A prospective, multiregional study. Lung Cancer 59: 246-254, 2008

118. Maas HA, Kruitwagen RF, Lemmens VE, et al: The influence of age and co-morbidity on treatment and prognosis of ovarian cancer: A population-based study. Gynecol Oncol 97:104-109, 2005

119. Nguyen PL, Chen M-H, Beard CJ, et al: Comorbidity, body mass index, and age and the risk of nonprostate-cancer-specific mortality after a post-radiation prostate-specific antigen recurrence. Cancer 116:610-615, 2010

120. Kim WY, Sharpless NE: The regulation of INK4/ARF in cancer and aging. Cell 127:265-275, 2006

121. Wiencke JK, Zheng S, Lafuente A, et al: Aberrant methylation of p16INK4a in anatomic and gender-specific subtypes of sporadic colorectal cancer. Cancer Epidemiol Biomarkers Prev 8:501-506, 1999

122. Li X, Hui A, Sun L, et al: P16INK4A hypermethylation is associated with hepatitis virus infection, age, and gender in hepatocellular carcinoma. Clin Cancer Res 10:7484-7489, 2004

123. Firoz EF, Warycha M, Zakrzewski J, et al: Association of MDM2 SNP309, age of onset, and gender in cutaneous melanoma. Clin Cancer Res 15:2573-2580, 2009

124. Yancik R, Ershler W, Satariano W, et al: Report of the National Institute on Aging Task Force on Comorbidity. J Gerontol A Biol Sci Med Sci 62:275-280, 2007

125. Balducci L, Tam-McDevitt J, Hauser R, et al: Long overdue: Phase II Studies in Older Cancer Patients: Where Does the FDA Stand? J Clin Oncol 26:1387-1388, 2008

126. Kornblith AB, Kemeny M, Peterson BL, et al: Survey of oncologists' perceptions of barriers to accrual of older patients with breast carcinoma to clinical trials. Cancer 95:989-996, 2002

