Cancer in North Carolina

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Tar Heel Footprints in Health Care

A periodic feature that recognizes individuals whose efforts—often unsung—enhance the health of North Carolinians

Tami Kittrell

Tami Kittrell, a senior administrative assistant at Aetna, Inc., in High Point, North Carolina, received a phone call on Thursday, April 29, 2010, that drastically altered her life. Learning that she had been diagnosed with T-cell lymphoma, Kittrell recalls that she initially felt confused and devastated, and at first she only told selected friends and family members about her diagnosis. In the following weeks, she spent hours researching her diagnosis on the Internet and searching for patient support groups. After starting treatment, Kittrell learned about The Leukemia & Lymphoma Society (LLS), the world’s largest voluntary health agency committed to blood cancer. She contacted the LLS national office and asked to be connected with a fellow patient for peer support, which was provided through the Patti Kauffman Robinson First Connection program, and she took advantage of LLS’s financial support resources.

Kittrell also attended her first Light the Night Walk, an LLS fundraiser event, in the Piedmont in 2011. Kittrell had participated in other walking events over the past 15 years but says that this was the first walk to which she truly felt connected.

In 2012 Kittrell started to increase her involvement with the North Carolina chapter of LLS. Through the Aetna Employees Reaching Out (AERO) program, Kittrell served as a team push captain for the Light the Night Walk in 2012, 2013, and 2014. The AERO program supports Aetna employees as they raise money for charities, and the program donates monthly proceeds to specific causes.

Since 2012 Kittrell has held numerous fundraising events including yard sales, Zumbathons, and giveaways. To date, Kittrell has raised over $5,000 for LLS. She also engages family and friends by raising awareness about leukemia and lymphoma, because most people know less about these cancers than they do about breast cancer or lung cancer. Recently she was invited to Capitol Hill to attend national LLS advocacy training and to speak to legislators in support of House Bill 460 and Senate Bill 2827, which would cap the prices of cancer medications.

Loreal Massiah, the manager of patient access, education, and advocacy at the North Carolina branch of LLS, lauds Kittrell’s work, saying “[Kittrell] has been a magnificent volunteer at our local chapter of The Leukemia & Lymphoma Society. She has worked diligently with our chapter to raise research funds at our Light the Night Walk and has advocated on behalf of all patients by sharing her personal story on Capitol Hill to help all patients access quality affordable care.”

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Address correspondence to Elizabeth Chen, North Carolina Institute of Medicine, 630 Davis Dr, Ste 100, Morrisville, NC 27560 (Liz_Chen@nciom.org).
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Health Care Utilization From Chemotherapy-Related Adverse Events Among Low-Income Breast Cancer Patients: Effect of Enrollment in a Medical Home Program


BACKGROUND Chemotherapy-related health care utilization by breast cancer patients can be expensive for payers and patients. This study evaluated the patient-centered medical home program Community Care of North Carolina (CCNC) in terms of its potential to reduce health care utilization associated with chemotherapy-related adverse events (AEs).

METHODS Early-stage breast cancer cases diagnosed during the 5-year period 2003–2007 were identified in the North Carolina Central Cancer Registry; these cases were then linked to North Carolina Medicaid claims data. We measured health care utilization associated with chemotherapy-related AEs by setting (inpatient, outpatient, or emergency department) during a 15-month postdiagnosis follow-up period. Descriptive and multivariate analyses were performed to examine associations between CCNC enrollment and health care utilization associated with chemotherapy-related AEs.

RESULTS A large proportion of breast cancer patients had at least 1 health care visit associated with a chemotherapy-related AE (n = 412 [72.3%]). The mean numbers of AE-related visits occurring in inpatient, outpatient, and emergency department settings were 0.30 (standard deviation [SD] = 0.83), 6.92 (SD = 10.94), and 0.46 (SD = 1.26), respectively. CCNC enrollment was associated with significantly fewer inpatient admissions (marginal effect, −0.1421; 95% confidence interval, −0.280 to −0.004).

LIMITATIONS In this observational study, we were unable to draw conclusions about the causality of these associations.

CONCLUSIONS Patients enrolled in CCNC had fewer inpatient health care visits associated with chemotherapy-related AEs. Future research should continue to explore the extent to which patient-centered medical homes can monitor and help manage the effects of cancer treatments.

Breast cancer, which is the most common type of cancer in women, made up more than one-third of all new cancers diagnosed among women in North Carolina in 2011 [1]. The 5-year incidence rate of female breast cancer per 100,000 population in North Carolina increased from 148.2 in 2001 to 157.4 in 2011; during the same period, the rate of mortality from breast cancer decreased from 26.5 to 22.8 per 100,000 persons [1]. The growing incidence of breast cancer in North Carolina, the increasing number of breast cancer survivors, and the aging of the US population mean that the demand for breast cancer care will likely increase, and we must consider how to ensure that the health care system is prepared to respond to this demand.

Although most of the health care utilization by cancer patients is associated with diagnostic and therapeutic management of the disease, management of chemotherapy-related adverse events (AEs) also requires substantial resources [2]. Several studies have shown that treatment-related AEs are associated with substantial costs resulting from higher rates of inpatient and emergency department (ED) admissions [3–5]. A few observational studies of breast cancer patients have shown that chemotherapy-related AEs have an enormous impact on health care expenditures and utilization [6, 7].

The effective management of chemotherapy-related AEs can be facilitated by community care management programs such as the patient-centered medical home (PCMH) model (also known as the primary care medical home model); integrating such a model into cancer care can enable more efficient utilization of available health care resources. PCMHs are designed to improve health care quality, to coordinate patient care across multiple providers, and to reduce the need for inappropriate or avoidable utilization of hospital EDs and inpatient beds [8]. In North Carolina, Community Care of North Carolina (CCNC) was established to provide care coordination, management, and prevention services for Medicaid beneficiaries [9]. Medicaid beneficiaries voluntarily enroll in the CCNC program and select a PCMH provider from the list of primary care providers serving their area; this provider is expected to coordinate the overall health care needs of that beneficiary, with support...
from a medical management team [10]. The CCNC program focuses on patients who are moving across care settings and provides transitional support services such as face-to-face counseling during inpatient admission, medication reconciliation after discharge, self-management training, and other types of patient education. The ultimate goal of this PCMH program is to promote better health outcomes in primary care settings, thereby reducing the utilization of inpatient and ED services.

To our knowledge, there are no studies assessing the impact of CCNC on health care utilization associated with cancer treatment–related AEs. Specifically, we lack data on the role that CCNC plays in the care of breast cancer patients experiencing chemotherapy-related AEs. Hence, the specific aims of this study were to describe the extent of health care utilization associated with chemotherapy-related AEs in the Medicaid breast cancer population in North Carolina and to assess the relationship between CCNC enrollment and utilization of such health care.

Methods

Data Sources

The North Carolina Integrated Cancer Information and Surveillance System (ICISS) provided access to cancer registry data and Medicaid claims data, diagnostic and procedural code lookup libraries, and analytic support for this study. [Editor’s note: For more information about ICISS, refer to the commentary by Meyer and colleagues on pages 265-269]. Specifically, North Carolina Central Cancer Registry (NCCCR) data were used to identify women diagnosed with early-stage breast cancer from January 1, 2003, through December 31, 2007. These data include clinical information relevant to the diagnosed cancer, such as primary site and tumor staging. The NCCCR data were then linked to Medicaid claims to identify women who were insured by Medicaid during this period. The Medicaid claims data provide details about health care utilization, including service dates, which allowed us to perform a longitudinal assessment of postdiagnosis treatments and health outcomes.

Cohort Selection

Our study sample consisted of women aged 18–64 years who had a diagnosis of early-stage breast cancer (stage 0, I, or II) based on the presence in the NCCCR data of an International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) code of 174.X, 238.3, or 239.3. Eligible women had to have been enrolled in Medicaid for at least 1 month before their index diagnosis, and they must not have had evidence of cancer prior to that time. We excluded cases diagnosed at autopsy or on a death certificate, cases with missing or unknown tumor stage data, and cases with an additional cancer diagnosis reported in the registry within 1 year of the index diagnosis. Because Medicaid enrollment can be transient [11], we only included patients who had at least 12 months of Medicaid enrollment during the 15-month postdiagnosis period, so that most of their service claims could be captured. These exclusions followed a protocol that we described previously in another paper [10]. We further excluded patients who were eligible to receive both Medicare and Medicaid benefits, because complete treatment claims for these patients were not available. See Figure 1 (online version only) for the numbers of patients involved at each stage of the selection process.

Figure 1. Process of Selecting the Final Study Sample

This figure is available in its entirety in the online edition of the NCMJ.

Definition and Measurement of Variables

Cancer treatments. Breast cancer treatments (surgery, chemotherapy, radiation therapy, and hormone therapy) were identified using the codes listed in Appendix 1 (online version only). Binary variables—which were not mutually exclusive—were created to define receipt of each of these types of treatments at any time during the study period.

Health care visits associated with chemotherapy-related AEs (dependent variable). Because chemotherapy is the principal source of AEs in the breast cancer patient population, we specifically focused on these AEs. For the purpose of this study, we included moderate-to-severe chemotherapy-related AEs experienced by breast cancer patients as reported in other studies [7, 12]. Following the approach of Hassett and colleagues [7], we grouped these AEs into 8 categories: abnormal electrolyte levels or dehydration; constitutional symptoms and nonspecific symptoms associated with chemotherapy; nausea, emesis, and diarrhea; infection and fever; malnutrition; anemia and transfusion of red blood cells; neutropenia or thrombocytopenia; and deep vein thrombosis or pulmonary embolism. The codes for these AEs are listed in Appendix 1 (online version only).

It is important to note that these AEs are not 100% specific to the receipt of chemotherapy and may occur in breast cancer patients who did not receive chemotherapy. In order to be consistent with and allow comparisons to the published literature, we used the algorithm developed by Hassett and colleagues [7] to define this type of health care utilization, and we use the term “chemotherapy-related AEs” in our study; however, we also attempted to parse out the occurrence of these events in patients who did not receive chemotherapy. Patients diagnosed with stage 0 breast cancer were included in our analysis because we observed that a significant proportion (nearly 22%) of these patients received chemotherapy during the study period; thus, they were likely to have experienced clinically relevant AEs.

A patient was considered to have experienced a chemotherapy-related AE when an inpatient, outpatient, or ED claim indicated that any of the above-mentioned AEs had
been reported using a relevant procedure code, ICD 9-CM code, or diagnosis-related group (DRG) code. Because the first-listed diagnosis code on the claim does not necessarily represent the reason for the visit [13], mostly because of intercoder variations in practice, all available diagnosis code fields (up to 9) were used. Health care visits during which a patient received cancer treatments such as chemotherapy or radiation therapy were excluded. The primary outcome variables were the total number of visits to each of the 3 health care settings.

**CCNC enrollment (primary independent variable).** Because CCNC networks and primary care providers receive a per-member-per-month (PMPM) payment from Medicaid to coordinate the health and disease management needs of the enrolled population, patients were considered to be enrolled in the CCNC program (and thus to have a PCMH) when both the network and the provider management fees were paid on a monthly basis. We identified the PMPM payment using state-defined procedure codes (W9920 or W9921 for the provider and W9923 for the network) [14]. A binary variable representing patients who had any CCNC enrollment during the 15-month postdiagnosis period served as the primary independent variable.

**Control variables.** The sociodemographic control variables were sex, race (non-Hispanic white, non-Hispanic black, or other), rural/urban status of the county of residence, and whether or not Medicaid eligibility was due to blindness or disability.

Clinical control variables included cancer stage and comorbidity index, the latter of which was determined using a previously described [10, 15] modification of the National Cancer Institute Combined Index algorithm. Cancer stage was derived using the American Joint Committee on Cancer (AJCC) stage grouping, if possible; the Surveillance, Epidemiology, and End Results (SEER) summary staging was used if AJCC stage grouping was not available, or tumor, node, and metastasis (TNM) staging was used if neither AJCC stage grouping nor SEER summary staging was available [16].

**Statistical Analysis**

Bivariate analyses were performed to compare the characteristics and mean numbers of visits for chemotherapy-related AEs, by type of health care setting, for patients who had ever been enrolled in CCNC versus those who had never been enrolled in CCNC. Because of the lack of specificity of chemotherapy-related AEs, we also used bivariate statistics to compare the frequency with which patients experienced each type of AE and their chemotherapy status (ie, whether they received chemotherapy during the study period or not). Chi-square and Fisher’s exact tests were used for comparing categorical variables, and t tests were used for comparing continuous variables.

We used a method proposed by Long and Freese [17] to select an appropriate analytic model with which to perform multivariate analyses for our continuous outcome measures (see Figure 2; online version only). We chose negative binomial regression for our analytic model, because it fit the observed data best, and it took into account the possibility of AEs occurring in patients who were not receiving chemotherapy [18].

**FIGURE 2.** Comparison of Predicted Probabilities of Health Care Visit Counts From 3 Statistical Modeling Approaches With the Observed Data, Depicted as Deviation From the Observed Proportion, Based on a Method Proposed by Long and Freese [17]

Three separate regression analyses were performed to estimate health care utilization; outcomes were the number of inpatient visits associated with chemotherapy-related AEs, the number of outpatient visits associated with chemotherapy-related AEs, and the number of ED visits associated with chemotherapy-related AEs. We used an alpha level of 0.05 to determine statistical significance. Results are presented as average marginal effects (MEs), which represent the marginal change in the number of visits induced by changes in each independent variable [19]. For instance, for our primary independent variable (CCNC enrollment), the ME would indicate the increase or decrease in the number of inpatient admissions associated with chemotherapy-related AEs for patients who were enrolled in CCNC compared with those who were not enrolled in CCNC. Modeling was performed using Stata statistical software [20].

**Results**

A total of 570 breast cancer patients met the inclusion criteria and were included in the analysis. The average age of patients in the sample was 48.4 years (standard deviation [SD] = 8.9); the sample included an almost equal proportion of white patients (43.0%) and black patients (44.4%); and the majority of patients (65.3%) lived in an urban area. Fifty-four percent of patients in the sample were enrolled in CCNC for at least 1 month during the study period; among patients with any enrollment, the mean duration of enrollment was 10.8 months. Table 1 summarizes the demographic and clinical characteristics of patients by CCNC enrollment status. Enrollment in CCNC was more common among younger women (P<.001) and among those who were black (P=.005).

Nearly three-fourths (n = 412 [72.3%]) of the patients in the sample had at least 1 health care visit associated with a chemotherapy-related AE during the 15-month follow-up period; specifically, 19.1% had at least 1 inpatient admission, 69.6% had at least 1 outpatient visit, and 24.9% had at least 1 ED visit. The mean numbers of visits associated with chemotherapy-related AEs during the follow-up period were
0.30 for inpatient admissions (SD = 0.83; range, 0–8), 6.92 for outpatient visits (SD = 10.94; range, 0–75), and 0.46 for ED visits (SD = 1.26; range, 0–15). Patients enrolled in CCNC had fewer overall visits associated with chemotherapy-related AEs across all 3 health care settings, but the differences were not statistically significant in the bivariate analysis (see Figure 3).

Table 2 shows the numbers and percentages of patients who experienced each type of chemotherapy-related AE during the study period, by chemotherapy status (received chemotherapy or did not receive chemotherapy).

Table 3 shows the average ME of CCNC enrollment and other covariates on health care utilization (inpatient, outpatient, and ED visits) associated with chemotherapy-related AEs. CCNC enrollment was associated with significantly fewer inpatient admissions for chemotherapy-related AEs (ME, -0.14; 95% confidence interval, -0.280 to -0.004). Our analysis did not find any significant association between CCNC enrollment and the number of outpatient or ED visits for chemotherapy-related AEs. Age at diagnosis and black race were significantly associated with fewer outpatient visits for chemotherapy-related AEs. Higher comorbidity score, receipt of chemotherapy, and receipt of surgery were significantly associated with a greater number of health care visits for chemotherapy-related AEs across all 3 health care settings.

**Discussion**

To our knowledge, this is the first study to investigate the role of PCMHs in managing chemotherapy-related AEs among women who were recently diagnosed with breast cancer. In this study, we describe the extent of health care utilization associated with chemotherapy-related AEs among early-stage breast cancer patients insured by Medicaid. We found that these patients commonly experienced many of the AEs typically associated with chemotherapy—including abnormal electrolyte levels, dehydration, nausea, emesis, and diarrhea—all of which can be proactively monitored.
and managed during and after chemotherapy in coordinated care settings such as a PCMH. CCNC’s patient-centered approach to providing transitional support and facilitating follow-up care in primary care settings gives it an advantage over other care delivery systems.

The proportions of patients seeking health care for chemotherapy-related AEs were higher in our study than in the study by Hassett and colleagues (19% versus 12% for hospitalizations; 25% versus 6% for ED visits) [7]. This could be because of differences between the 2 studies in population characteristics and/or duration of follow-up (15 months versus 12 months). Also, the Medicaid patient population has higher rates of hospitalization for conditions that can often be treated outside of the hospital or avoided altogether [21, 22], compared with Medicare populations that have been studied previously.

<table>
<thead>
<tr>
<th>Patients experiencing AE (N = 570)</th>
<th>Did not receive chemotherapy (n = 252)</th>
<th>Received chemotherapy (n = 318)</th>
<th>P-value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abnormal electrolyte levels or dehydration</td>
<td>25 (10%)</td>
<td>76 (24%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Constitutional symptoms and nonspecific symptoms associated with therapy†</td>
<td>60 (24%)</td>
<td>117 (37%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Nausea, emesis, and diarrhea</td>
<td>36 (14%)</td>
<td>179 (56%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Infection and fever</td>
<td>57 (23%)</td>
<td>110 (35%)</td>
<td>&lt;.002</td>
</tr>
<tr>
<td>Malnutrition</td>
<td>7 (3%)</td>
<td>25 (8%)</td>
<td>&lt;.009</td>
</tr>
<tr>
<td>Anemia and red blood cell transfusion</td>
<td>41 (16%)</td>
<td>151 (47%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Neutropenia or thrombocytopenia</td>
<td>6 (2%)</td>
<td>134 (42%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Deep vein thrombosis/pulmonary embolism</td>
<td>1 (&lt;1%)</td>
<td>6 (2%)</td>
<td>.109</td>
</tr>
<tr>
<td>Total</td>
<td>133 (53%)</td>
<td>279 (88%)</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>

*P-values were based on chi-square test, or on Fisher’s exact test if cell counts were less than 30.
†Includes symptoms such malaise, fatigue, dizziness, or syncope.
In our study, North Carolina breast cancer patients who were enrolled in CCNC had fewer overall health care visits associated with chemotherapy-related AEs than did patients who were not enrolled in CCNC; this finding was clinically and statistically significant for inpatient admissions but not for outpatient visits or ED visits. Because inpatient admissions are costly to the North Carolina health care system and may represent more severe AEs, our findings suggest an important potential value of CCNC’s efforts to improve coordination of care and to ensure timely access to primary care providers. This finding is consistent with the general expectation that medical care is more often provided in the outpatient setting in a PCMH model, thus increasing outpatient utilization and decreasing inpatient admissions and ED use.

Interestingly, we observed a negative association between age at diagnosis and the number of AEs (ie, there were fewer AEs with older age). One possible explanation for this finding could be that younger breast cancer patients tend to present with more advanced tumors that require more aggressive treatment [23-25]; hence, these patients may be more likely to experience a chemotherapy-related AE that leads to 1 or more health care visits.

Like previous studies [6, 7], our study found a significantly positive association between the overall number of health care visits associated with AEs and several other factors: cancer stage, the presence of comorbidities, and receipt of chemotherapy. Our finding that a sizeable proportion of stage 0 patients received chemotherapy may indicate that these patients were initially diagnosed at stage 0 but later progressed to a more advanced stage, at which time they were deemed appropriate candidates for chemotherapy. Unfortunately, we cannot verify this hypothesis, because NCCCR data only record cancer stage at incident diagnosis. Other possibilities are that these stage 0 patients may have been found to have HER2-positive tumors, or they may have had high Oncotype Dx scores.

Our study has several limitations. First, Medicaid claims data include up to 9 diagnosis codes for each health care visit, which may lead to an underestimation of the true number of AEs. Second, our study did not account for the potential confounding effects of other factors, such as socioeconomic status, insurance coverage, and patient education. Third, our study was based on a retrospective analysis of claims data, which may be subject to information bias and recall bias. Despite these limitations, our study provides valuable insights into the impact of CCNC enrollment on health care utilization and the potential value of coordinated care models in reducing chemotherapy-related AEs and improving patient outcomes.
provide care management and coordination of care; this could have led to a possible overestimation of health care utilization associated with chemotherapy-related AEs. In the absence of patient- or provider-reported data about the visit, we have no way of knowing whether this is the case. Second, in the absence of patients’ medical records, we did not have detailed contextual information about communication with and recommendations of providers, or about any sentinel events leading up to and possibly influencing the visit. Third, because of unavailability of data, we were unable to include patients with stage III breast cancer, who are also suitable candidates for chemotherapy and may therefore experience chemotherapy-related AEs. Finally, because this was an observational study, we cannot draw any conclusions about the causality of these associations.

Despite these limitations, our study provides important and timely information about the extent of health care utilization associated with chemotherapy-related AEs, and it suggests that care management programs such as CCNC may reduce the number of health care visits associated with chemotherapy-related AEs. In the context of an aging population and rising cancer-related health care costs, these findings have important implications for estimating health care demand and for containing health care costs in North Carolina [26].

Providing high-quality cancer care for economically disadvantaged populations is challenging for several reasons, including gaps in communication, poor access to primary care, and lack of post-treatment coordination of care [27]. In addition, disadvantaged patients may be less able to self-manage their condition and to meet their post-treatment health care needs [28]. The importance of innovative interventions that can bridge these gaps, facilitate optimum care of breast cancer patients, and maintain quality of care cannot be overemphasized under current economic conditions, given the increasing demand for care and shortages of providers. PCMHs are equipped to improve communication and to provide care management and coordination of care [29, 30]; thus, they can help providers to meet these challenges more effectively when caring for breast cancer survivors.

PCMHs have proven to be effective in improving outcomes for patients with chronic diseases such as asthma, diabetes, and cardiovascular conditions [14, 31-33]. As we have reported elsewhere [10], breast cancer survivors who were enrolled in CCNC were significantly more likely to receive guideline-concordant follow-up care. By virtue of their patient-centered primary care approach, CCNC and other PCMH programs hold huge potential for reducing costs (by proactively managing treatment-related AEs in a primary care setting) and for reducing preventable inpatient admissions and ED visits. The results of this study, although based on North Carolina Medicaid data, provide relevant information to providers and policymakers and should encourage PCMH initiatives nationwide. In this study we showed that any CCNC enrollment during the 15-month postdiagnosis period may decrease health care utilization associated with chemotherapy-related AEs, but future studies could investigate how the duration and intensity of CCNC participation affect health care utilization among cancer patients. Future research also should continue to explore the extent to which PCMHs can help to coordinate survivorship care and to monitor and manage late effects of cancer treatments.

Ravi K. Goyal, MS, BPharm health outcomes scientist, RTI Health Solutions, Research Triangle Park, North Carolina; research associate, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Stephanie B. Wheeler, PhD, MPH faculty member, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill; assistant professor, Department of Health Policy and Management, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Racquel E. Kohler, MSPH doctoral student and predoctoral fellow, Department of Health Policy and Management, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Kristen H. Lich, PhD, MHS assistant professor, Department of Health Policy and Management, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Ching-Ching Lin, MHS doctoral student and predoctoral fellow, Department of Health Policy and Management, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Katherine Reeder-Hayes, MD, MBA assistant professor, Division of Hematology and Oncology, School of Medicine, University of North Carolina at Chapel Hill; faculty member, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Anne-Marie Meyer, PhD facility director, Integrated Cancer Information and Surveillance System (ICISS), Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Deborah K. Mayer, PhD, AOCN, FAAN director of cancer survivorship, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill; associate professor, UNC School of Nursing, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

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References


Effects of Distance to Care and Rural or Urban Residence on Receipt of Radiation Therapy Among North Carolina Medicare Enrollees With Breast Cancer

Stephanie B. Wheeler, Tzy-Mey Kuo, Danielle Durham, Brian Frizzelle, Katherine Reeder-Hayes, Anne-Marie Meyer

BACKGROUND Distance to oncology service providers and rurality may affect receipt of guideline-recommended radiation therapy (RT), but the extent to which these factors affect the care of Medicare-insured patients is unknown.

METHODS Using cancer registry data linked to Medicare claims from the Integrated Cancer Information and Surveillance System (ICISS), we identified all women aged 65 years or older who were diagnosed with stage I, II, or III breast cancer from 2003 through 2005, who had Medicare claims through 2006, and who were clinically eligible for RT. We geocoded the address of each RT service provider’s practice location and calculated the travel distance from each patient’s residential address to the nearest RT provider. We used ZIP codes to classify each patient’s residence as rural or urban according to rural-urban commuting area codes. We used generalized estimating equations models with county-level clustering and interaction terms between distance categories and rural-urban status to estimate the effect of distance to care and rural-urban status on receipt of RT.

RESULTS In urban areas, increasing distance to the nearest RT provider was associated with a lower likelihood of receiving RT (odds ratio [OR] = 0.54; 95% confidence interval [CI], 0.30–0.97) for those living more than 20 miles from the nearest RT provider compared with those living less than 10 miles away. In rural areas, those living within 10–20 miles of the nearest RT provider were more likely to receive RT than those living less than 10 miles away (OR = 1.73; 95% CI, 1.08–2.76).

LIMITATIONS Results may not be generalizable to areas outside North Carolina or to non-Medicare populations.

CONCLUSIONS Coordinated outreach programs targeted differently to rural and urban patients may be necessary to improve the quality of oncology care.

Differences in the quality of breast cancer care, which can directly influence health outcomes, have been documented across different settings and subpopulations [1-5]. A variety of patient, provider, and health system factors can contribute to poor-quality cancer care [6-10]. An underappreciated factor that influences quality of care is access to oncology service providers [11, 12]. Cancer patients who must travel long distances to reach oncology care providers are potentially at high risk of going untreated or being undertreated [11, 13-15]. In addition, differential availability of resources such as transportation across rural and urban settings may contribute to differences in the quality of care patients receive [16, 17]. Treatments that require frequent visits to a provider, such as radiation therapy (RT), may be particularly sensitive to geographic barriers. The extent to which distance to care and rurality influence receipt of guideline-recommended RT by breast cancer patients in North Carolina is unknown.

Distance to care has been shown to affect receipt of appropriate cancer screening and treatment in a variety of settings [10, 11, 18-26]. However, studies of the relationship between distance to care and cancer care utilization have been inconsistent, possibly due to variability in how distance to care is measured. In addition, such variation may be greater in suburban and rural areas than in urban areas [27, 28]. To our knowledge, no published studies have evaluated the impact of distance to care and rurality on receipt of breast cancer treatment in North Carolina. Because North Carolina is a large, diverse state with a variety of rural and urban environments, it is important to understand how quality of care for breast cancer varies across these settings.

In light of these gaps and to understand barriers to care in North Carolina, we sought to examine geographic variables and receipt of care. Specifically, we assessed whether the distance to oncology service providers and rural or urban residence explained a portion of the variation in receipt of adjuvant RT among Medicare-insured breast cancer patients who had completed surgery.
Methods

Data sources. For our analyses, we employed a novel data resource, the North Carolina Integrated Cancer Information and Surveillance System (ICISS). [Editor’s note: For more information about ICISS, refer to the commentary by Meyer and colleagues on pages 265-269]. This statewide, population-based data set includes cancer registry data and multipayer insurance claims data; because of its richness and comprehensiveness, ICISS is uniquely suited to evaluate distance to care and quality of care. ICISS covers a wide variety of geographic subregions, with varying densities and distributions of populations and health care facilities, and it includes physician identifiers and geocoded patient and physician locations. The cancer registry data provide detailed clinical information about cancer diagnosis, stage, grade, and biomarker status, as well as demographic information about patients. The Medicare claims data include demographic information and details about any health care services or procedures for which an insurance claim was filed, along with corresponding diagnoses.

Cohort selection. We created a retrospective cohort that included women diagnosed with breast cancer between January 1, 2003, and December 31, 2005 whose records could be linked to Medicare insurance claims. Using the North Carolina Central Cancer Registry (NCCCR), we identified all women aged 65 years or older who were diagnosed with stage I, II, or III breast cancer from 2003 through 2005; we then linked these patient records to Medicare claims data to identify services and procedures received from 3 months before diagnosis through 1 year after diagnosis. To identify women who clearly met clinical guidelines for RT [29, 30], we limited our sample to women who had undergone breast-conserving surgery or who had undergone mastectomy and had tumors larger than 5 cm, using claims-based definitions from prior research [10, 31]. Although women with lymph-node-positive disease are also candidates for RT, we chose to focus specifically on indications for RT of the breast rather than RT of the axilla.

Using the registry, we obtained records for 7,653 women with breast cancer that was newly diagnosed from 2003 through 2005. We then excluded patients diagnosed at death (n = 7); patients without complete claims from 3 months before through 12 months after diagnosis (n = 1,987); patients with stage 0, stage IV, or unstaged disease (n = 1,608); patients who did not meet clinical criteria for RT (n = 516); and patients with end-stage renal disease (n = 1). Among the remaining women, we further limited our sample to women who had undergone breast-conserving surgery (n = 1,798) or women who had undergone mastectomy and had tumors larger than 5 cm (n = 140).

Measurement of RT (dependent variable). We used Medicare claims to determine whether RT was ever received within 1 year of diagnosis, as was done in prior studies [10, 32]. We used the procedure codes listed in Table 1 to identify surgeries and RT performed following a breast cancer diagnosis.

Measurement of distance to care (independent variable). To enable calculation of distance to RT providers, we identified all physicians in the claims database who provided RT to Medicare-insured breast cancer patients from 2003 through 2005. Using the physicians’ unique physician identification numbers (assigned by Medicare), we obtained physician address information from the Registry of Medicare Physician Identification and Eligibility Records. We then used this information to build a master list of all physicians providing RT to breast cancer patients in North Carolina and the physicians’ addresses.

Patient addresses were geocoded by NCCCR, following guidelines published by the North American Association of Central Cancer Registries [33]. In this study, the initial geocoding of physician addresses was performed by Mapping Analytics, a firm that provides custom mapping and analysis services. The remaining unmatched addresses (approximately 15%) were cleaned and geocoded using Esri ArcGIS 10.1 software [34], which increased the match rate to greater than 95%. Road network distances were then computed from every patient in the sample to every phy-

<table>
<thead>
<tr>
<th>TABLE 1. Codes Used to Identify Breast Cancer Treatments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of code</strong></td>
</tr>
<tr>
<td>Code for aggressive mastectomy</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Code for breast-conserving surgery</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>Code for radiation therapy</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td>ICD-9-CM diagnosis codes V58.0, V66.1, V67.1</td>
</tr>
</tbody>
</table>

sician in the state who provided RT to Medicare enrollees with breast cancer. These distances were calculated using Esri’s StreetMap Premium for ArcGIS to identify road networks between the patient and the physician. Distance to nearest provider was defined as the shortest road-network path from the patient’s address to that of the nearest RT provider.

We also computed Euclidean (straight-line) distances between providers and patients using the GEODIST function of SAS software [35]. We examined both the Euclidean and road-network measurements of distance to care and explored differences between them, but we opted to focus on road-network distances only, as they are known to be more accurate [28, 36]. We chose to measure the shortest distance rather than the shortest travel time because distance (based on the length of the road features in the GIS data set) is a more reliable measure than time calculations (based on imprecise speed attributes assigned to road segments). We examined multiple specifications of distance in sensitivity analyses, including distance measured continuously and in 5-mile and 10-mile categorical increments. We opted to use 10-mile categorical increments (less than 10 miles; 10–20 miles; and greater than 20 miles) in the primary analysis because they provided improved model fit statistics and larger cell sizes with less granular categorization (resulting in better model stability).

Classification of residence as rural or urban (independent variable). We used ZIP code information to determine whether each patient’s address was rural or urban according to the rural-urban commuting area (RUCA) codes crosswalk, version 2.0, created by the Rural Health Research Center [37]. We created a binary measure for rural-urban status following guidance from the Rural Health Research Center. The RUCA rural-urban classification system combines information about population and commuting relationships, and researchers have used this system to compare urban and rural differences in more detail than is possible using the county-level definition [38-41]. We interacted our categorical distance measures with rural-urban status to test whether the effect of distance to RT providers is different in rural areas than in urban areas.

Covariates. As was done in previously published research [10, 31, 32], we adjusted models to account for patient sociodemographic characteristics that have previously been shown to influence receipt of RT, including age (65–69 years; 70–74 years; 75–79 years; 80 years or older), race (nonwhite; white), marital status (married; not married), and state buy-in (whether the state pays the individual’s Medicare premiums, which serves as a binary proxy for low-income status) [42]. We also adjusted for important disease characteristics, including American Joint Commission on Cancer stage (stage I; stage II; stage III), hormone receptor status at diagnosis, which is based on whether the tumor has estrogen and/or progesterone receptors (negative; positive; or unknown), any prior cancer, and year of diagnosis. We recoded variables with missing data in order to retain as many observations as possible. For example, there were many women for whom the hormone receptor status of their tumor was unknown; therefore we created a separate category, “unknown.”

Using methods consistent with those described in previously published research [10, 31, 43], we adjusted for comorbidities identified from Medicare claims using the National Cancer Institute Combined Index, with some modification to allow us to capture comorbid conditions co-occurring during the cancer treatment period [44]. Specifically, comorbidity was measured according to the Charlson Index from 3 months prior to diagnosis through 12 months after diagnosis, and breast-cancer-specific weights were calculated for each condition [44].

Lastly, studies have shown that county-level characteristics may affect receipt of health care services [45-47]. Therefore, as has been done in other studies [48, 49], we controlled for the following sociodemographic characteristics at the county level: percentage of the population that is nonwhite, population density, and median household income, all of which were obtained from the Area Resource File published in 2000 by the Health Resources and Services Administration [50].

Analyses. We used descriptive statistics to examine distributions in the data, performed bivariate analyses employing chi-squared tests for categorical variables, and performed t tests for continuous variables. We then used a generalized estimating equations (GEE) model with logit link function, exchangeable working correlation, and county-level clustering to examine the effect of geospatial measures on receipt of RT after breast-conserving surgery, controlling for other known confounders. The GEE model obtains population-based estimates by accounting for variances in correlated data (ie, people living in the same county share county-level characteristics) [51]. Individuals residing in the same county are no longer considered independent observations; therefore a GEE model is appropriate for patients living in the same geographic area, who are expected to be more related (correlated) to one another than to those living in different areas. Without such adjustment, the variance estimates tend to produce biased and smaller standard errors, which can lead to biased conclusions.

To determine whether distance to care had different effects in urban areas than in rural areas, we included interaction terms between the rural-urban indicator variable and categorical distance variables, and we conducted a Wald test to determine the significance of the overall interaction effect. We calculated odds ratios (ORs) for our overall model and stratified by rural-urban residence. All analyses were conducted using SAS software version 9.3 software [35].

This study was approved by the institutional review board of the University of North Carolina at Chapel Hill.
Results

The final analysis sample included 1,938 patients living in 98 different counties in North Carolina, with between 1 and 131 women in each county. Overall, 65% of the women in the study sample received guideline-recommended RT. Table 2 presents the sample characteristics and the results of bivariate analyses, by receipt of RT. More than 50% of the women in our sample lived within 10 miles of a physician who provided RT. There were statistically significant differences in receipt of RT among the 3 distance-to-care categories and between rural residents and urban residents.

### Table 2.
Sample Characteristics and Bivariate Results by Radiation Therapy (RT) Status

<table>
<thead>
<tr>
<th>Variable</th>
<th>Total sample (N = 1,938)</th>
<th>Received RT (n = 1,253)</th>
<th>Did not receive RT (n = 685)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age group</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–69 years</td>
<td>534 (28%)</td>
<td>415 (33%)</td>
<td>119 (17%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>70–74 years</td>
<td>510 (26%)</td>
<td>358 (29%)</td>
<td>152 (22%)</td>
<td></td>
</tr>
<tr>
<td>75–79 years</td>
<td>480 (25%)</td>
<td>291 (23%)</td>
<td>189 (28%)</td>
<td></td>
</tr>
<tr>
<td>80 years or older</td>
<td>414 (21%)</td>
<td>189 (15%)</td>
<td>225 (33%)</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td>.10</td>
</tr>
<tr>
<td>White</td>
<td>1,655 (85%)</td>
<td>1,082 (86%)</td>
<td>573 (84%)</td>
<td></td>
</tr>
<tr>
<td>Nonwhite</td>
<td>283 (15%)</td>
<td>171 (14%)</td>
<td>112 (16%)</td>
<td></td>
</tr>
<tr>
<td><strong>Marital status</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Married</td>
<td>807 (42%)</td>
<td>588 (47%)</td>
<td>219 (32%)</td>
<td></td>
</tr>
<tr>
<td>Not married</td>
<td>1,131 (58%)</td>
<td>665 (53%)</td>
<td>466 (68%)</td>
<td></td>
</tr>
<tr>
<td><strong>State Medicare buy-in</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Buy-in</td>
<td>295 (15%)</td>
<td>155 (12%)</td>
<td>140 (20%)</td>
<td></td>
</tr>
<tr>
<td>No buy-in</td>
<td>1,643 (85%)</td>
<td>1,098 (88%)</td>
<td>545 (80%)</td>
<td></td>
</tr>
<tr>
<td><strong>AJCC stage at diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Stage I</td>
<td>1,181 (61%)</td>
<td>740 (59%)</td>
<td>441 (64%)</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>570 (29%)</td>
<td>363 (29%)</td>
<td>207 (30%)</td>
<td></td>
</tr>
<tr>
<td>Stage III</td>
<td>187 (10%)</td>
<td>150 (12%)</td>
<td>37 (5%)</td>
<td></td>
</tr>
<tr>
<td><strong>Hormone receptor status of tumor</strong></td>
<td></td>
<td></td>
<td></td>
<td>.20</td>
</tr>
<tr>
<td>ER/PR negative</td>
<td>144 (7%)</td>
<td>92 (7%)</td>
<td>52 (8%)</td>
<td></td>
</tr>
<tr>
<td>ER/PR positive</td>
<td>746 (38%)</td>
<td>465 (37%)</td>
<td>281 (41%)</td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>1,048 (54%)</td>
<td>696 (56%)</td>
<td>352 (51%)</td>
<td></td>
</tr>
<tr>
<td><strong>Year of diagnosis</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.001</td>
</tr>
<tr>
<td>2003</td>
<td>529 (27%)</td>
<td>379 (30%)</td>
<td>150 (22%)</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>803 (41%)</td>
<td>520 (42%)</td>
<td>283 (41%)</td>
<td></td>
</tr>
<tr>
<td>2005</td>
<td>606 (31%)</td>
<td>354 (28%)</td>
<td>252 (37%)</td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidity index score</strong></td>
<td>0.358</td>
<td>0.317</td>
<td>0.433</td>
<td>&lt;.001</td>
</tr>
<tr>
<td><strong>Prior cancer</strong></td>
<td></td>
<td></td>
<td></td>
<td>.10</td>
</tr>
<tr>
<td>Yes</td>
<td>325 (17%)</td>
<td>197 (16%)</td>
<td>128 (19%)</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>1,613 (83%)</td>
<td>1,056 (84%)</td>
<td>557 (81%)</td>
<td></td>
</tr>
<tr>
<td><strong>Urban or rural residence, at zip code level</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Urban</td>
<td>1,276 (66%)</td>
<td>857 (68%)</td>
<td>419 (61%)</td>
<td></td>
</tr>
<tr>
<td>Rural</td>
<td>662 (34%)</td>
<td>396 (32%)</td>
<td>266 (39%)</td>
<td></td>
</tr>
<tr>
<td><strong>Road network distance to nearest provider</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Less than 10 miles</td>
<td>1,075 (55%)</td>
<td>711 (57%)</td>
<td>364 (53%)</td>
<td></td>
</tr>
<tr>
<td>10–20 miles</td>
<td>425 (22%)</td>
<td>290 (23%)</td>
<td>135 (20%)</td>
<td></td>
</tr>
<tr>
<td>Greater than 20 miles</td>
<td>438 (23%)</td>
<td>252 (20%)</td>
<td>186 (27%)</td>
<td></td>
</tr>
<tr>
<td><strong>County-level predictors</strong></td>
<td></td>
<td></td>
<td></td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Mean % of population nonwhite</td>
<td>27.14</td>
<td>26.88</td>
<td>27.61</td>
<td>.28</td>
</tr>
<tr>
<td>Mean population density per square mile</td>
<td>364</td>
<td>379</td>
<td>336.4</td>
<td>&lt;.01</td>
</tr>
<tr>
<td>Median household income</td>
<td>$39,907</td>
<td>$40,241</td>
<td>$39,297</td>
<td>&lt;.01</td>
</tr>
</tbody>
</table>

Note. AJCC, American Joint Committee on Cancer; ER, estrogen receptor; PR, progesterone receptor.

*Medicare buy-in means that the state of North Carolina was paying the patient’s Medicare premiums; this was used as a proxy for low-income status.

*Hormone receptor status was classified as positive if the patient’s tumor had any estrogen receptors or progesterone receptors; it was classified as negative if the tumor had no estrogen receptors or progesterone receptors.

*The higher the comorbidity index score, the greater the number of comorbid conditions.
In general, women who received RT were younger, more likely to be married, and more likely to be higher-income compared with women who did not receive RT; women who received RT were also generally diagnosed in earlier study years, had cancer that was more advanced, and had fewer comorbid conditions. Women who lived in counties with a higher population density and/or higher median household income were also more likely to receive RT.

The results of multivariable analyses are presented in Table 3. With respect to distance to RT providers and rural-urban status, the results indicate significant interaction effects between these 2 variables (Wald statistic = 6.97; P<.05). In the subsample of urban patients, increasing distance to the nearest RT provider was significantly associated with lower odds of receiving RT (OR = 0.40; 95% confidence interval [CI], 0.30–0.76) for those living at least 20 miles from the nearest provider, compared with those living less than 10 miles from the nearest provider (see Table 4). In the subsample of breast cancer patients residing in rural areas, increasing distance to the nearest RT provider was significantly associated with higher odds of receiving RT (OR = 1.73; 95% CI, 1.08–2.76) for those living within 10–20 miles of the nearest RT provider compared with those living less than 10 miles from the nearest RT provider. For those living more than 20 miles from the nearest provider, distance did not significantly affect receipt of RT, compared with those living less than 10 miles from the nearest provider.

After controlling for all other factors, the odds of receiving RT were significantly higher for women who were married (OR = 1.40; 95% CI, 1.12–1.74) and for those diagnosed with stage III disease compared with stage I disease (OR = 2.93; 95% CI, 1.94–4.42). The odds of receiving RT were significantly lower for several groups of women: those older than 80 years compared with those aged 65–69 years (OR = 0.27; 95% CI, 0.21–0.35); those with lower incomes (OR = 0.66; 95% CI, 0.49–0.89); those diagnosed in 2004 compared with those diagnosed in 2003 (OR = 0.72; 95% CI, 0.56–0.92) or those diagnosed in 2005 compared with those diagnosed in 2003 (OR = 0.54; 95% CI, 0.35–0.82); and those with higher comorbidity scores (OR = 0.82; 95% CI, 0.70–0.98).

To further evaluate the robustness of the differential distance effect between urban and rural residence, we conducted a stratified analysis separating urban and rural samples while keeping all of the covariates in both models (results not shown). Statistically significant effects persisted in rural areas for the distance category of 10–20 miles, compared with less than 10 miles (OR = 1.76; 95% CI, 1.07–2.87). For urban areas, the significant finding for the distance category of greater than 20 miles, compared with less than 10 miles, becomes marginally significant (OR = 0.57; 95% CI, 0.32–1.02; Table 4). In addition, we grouped the distance categories in 5-mile increments and still found a significant distance effect in rural areas for the category of 15–20 miles, compared with less than 5 miles (OR = 2.14; Table 4).

### Table 3

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimated odds ratio (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>65–69 years (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>70–74 years</td>
<td>0.70 (0.52–0.94)</td>
<td>.02</td>
</tr>
<tr>
<td>75–79 years</td>
<td>0.47 (0.38–0.59)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>80 years or older</td>
<td>0.27 (0.21–0.35)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nonwhite (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>1.04 (0.79–1.38)</td>
<td>.762</td>
</tr>
<tr>
<td>Marital status</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not married (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Married</td>
<td>1.40 (1.12–1.74)</td>
<td>.003</td>
</tr>
<tr>
<td>State Medicare buy-ina</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No buy-in (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Buy-in</td>
<td>0.66 (0.49–0.89)</td>
<td>.006</td>
</tr>
<tr>
<td>AJCC stage at diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stage I (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Stage II</td>
<td>1.07 (0.89–1.30)</td>
<td>.452</td>
</tr>
<tr>
<td>Stage III</td>
<td>2.93 (1.94–4.42)</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Hormone receptor status of tumorb</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ER/PR negative (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>ER/PR positive</td>
<td>1.16 (0.68–1.96)</td>
<td>.585</td>
</tr>
<tr>
<td>Unknown</td>
<td>0.95 (0.55–1.63)</td>
<td>.845</td>
</tr>
<tr>
<td>Year of diagnosis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2003 (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>2004</td>
<td>0.72 (0.56–0.92)</td>
<td>.009</td>
</tr>
<tr>
<td>2005</td>
<td>0.54 (0.35–0.82)</td>
<td>.004</td>
</tr>
<tr>
<td>Comorbidity index score</td>
<td>0.82 (0.70–0.98)</td>
<td>.03</td>
</tr>
<tr>
<td>Prior cancer</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>0.96 (0.74–1.26)</td>
<td>.790</td>
</tr>
<tr>
<td>Urban or rural residence at ZIP code level</td>
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</tr>
<tr>
<td>Rural (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Urban</td>
<td>1.91 (1.23–2.96)</td>
<td>.004</td>
</tr>
<tr>
<td>Road network distance to nearest RT provider</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 10 miles (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>10–20 miles</td>
<td>1.73 (1.08–2.76)</td>
<td>.02</td>
</tr>
<tr>
<td>Greater than 20 miles</td>
<td>1.09 (0.73–1.63)</td>
<td>.662</td>
</tr>
<tr>
<td>Urban or rural residence and road network distance interaction</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rural x less than 10 miles (reference)</td>
<td>1.00</td>
<td></td>
</tr>
<tr>
<td>Urban x 10–20 miles</td>
<td>0.50 (0.27–0.94)</td>
<td>.03</td>
</tr>
<tr>
<td>Urban x greater than 20 miles</td>
<td>0.50 (0.24–1.02)</td>
<td>.058</td>
</tr>
<tr>
<td>County-level predictors</td>
<td></td>
<td></td>
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<tr>
<td>Mean % of population nonwhite</td>
<td>0.99 (0.98–1.01)</td>
<td>.313</td>
</tr>
<tr>
<td>Population density</td>
<td>0.99 (0.98–1.01)</td>
<td>.309</td>
</tr>
<tr>
<td>Median household income</td>
<td>1.00 (1.00–1.00)</td>
<td>.439</td>
</tr>
</tbody>
</table>

Note. AJCC, American Joint Committee on Cancer; CI, confidence interval; ER, estrogen receptor; PR, progesterone receptor.

*aMedicare buy-in means that the state of North Carolina was paying the patient’s Medicare premiums; this was used as a proxy for low-income status.

*bHormone receptor status was classified as positive if the patient’s tumor had any estrogen receptors or progesterone receptors; it was classified as negative if the tumor had no estrogen receptors or progesterone receptors.
In urban areas, we found a marginally significant effect for the distance category of greater than 20 miles, compared with less than 5 miles (OR = 0.55; 95% CI, 0.3–1.01).

Discussion

We examined receipt of RT as a metric that reflects the quality of breast cancer care and patients’ access to oncology service providers. We found that distance to care and rural-urban status were significantly associated with receipt of RT by breast cancer patients for whom RT was clinically indicated. Within urban areas, increasing distance to the nearest RT provider was generally associated with lower likelihood of receiving RT; in rural areas, living within 10–20 miles of the nearest RT provider was associated with greater odds of receiving RT, compared with living less than 10 miles from the nearest RT provider.

These findings may be explained in several ways. First, urban residents may be more likely to rely on public transportation than on personal transportation to reach health providers, and the burden of accessing care via this mode of transportation (which operates on set schedules) is likely to be greater as distance to care increases. In an urban area, living more than 20 miles away from the nearest RT provider may mean commuting an hour or more (via either public or personal transportation), and this may be an insurmountable barrier for elderly women with cancer.

In contrast, rural residents may be more likely to rely on personal transportation to access health care services and may be more accustomed to traveling longer distances for health care, because they often travel long distances to access other types of goods and services. As a result, people in the most remote rural areas (and by extension, those furthest from RT providers) may be more willing or able to drive further to access health care and other types of goods and services, and they may combine visits to health care providers with other errands. This supposition is supported by the research of Gesler and colleagues [52], who found that more than 85% of rural health care visits involved transportation by private car. Arcury and colleagues [17] found that in rural North Carolina, access to transportation—having a driver’s license or knowing someone who could provide transportation—was more important for health care utilization than distance to health care providers. In addition, residents of the most remote rural areas may be more willing to bypass the nearest RT provider in order to access oncology care at a larger, more centralized facility that is affiliated with a medical school or a cooperative group such as the Eastern Cooperative Oncology Group (ECOG), the National Surgical Adjuvant Breast and Bowel Project (NSABP), the North Central Cancer Treatment Group (NCCTG), or the Southwest Oncology Group (SWOG) [53, 54]. Our distance-to-care measure assessed distance to the nearest provider; as a next step in future analyses, it would be important to explore whether women living in the most remote areas are bypassing closer RT providers to obtain care at a larger health care facility and, if so, how far they are traveling to do so.

The interaction effects between distance to care and rural-urban residence suggest that rural and urban settings in North Carolina differ in terms of how distance to a health care provider affects access to care. These findings imply a need to consider these settings differently when planning interventions. Specifically, cancer patients living in urban environments may benefit from dedicated buses that transport multiple patients to and from RT (and chemotherapy) appointments, organized carpools, or public transportation vouchers. Experience suggests that such programs are fragmented, often poorly organized, and unevenly distributed across providers and patients. In contrast, cancer patients living in rural areas, who are accustomed to driving themselves to RT and other health care appointments, may benefit from parking vouchers and reimbursement for gasoline. Because it may not be pragmatic or logistically feasible to organize group transportation for patients living in disparate and remote rural areas, and because our research suggests that factors beyond distance to care may present greater barriers for rural women, efforts should focus on targeting assistance to the most vulnerable rural patients (eg, women who are poor, older, and/or socially isolated). Community-based nonprofit organizations, cancer support networks, insurers/payers, and health care facilities may be able to pool resources to support such initiatives. Both large academic cancer centers and smaller community-based RT practices can play major roles in helping to coordinate and facilitate such options for patients in North Carolina.

Additional nonclinical factors—such as older age, being unmarried, and low-income status—were significantly associated with lack of RT, a finding that is consistent with the results of prior studies [2, 10, 32, 55]. Patients in these categories are likely to be more vulnerable, and they may require more intensive outreach, support, and resources to help ensure they receive guideline-recommended RT. Among women who lived near an RT provider yet did not receive RT, unmeasured factors—such as social isolation, lack of transportation, and frailty—may have prevented them from accessing RT despite the geographic nearness of providers [16].

Secondary, administrative, and linked data analyses have several inherent limitations. First, registry-linked claims data do not reveal anything about patient-provider communication in decision making; therefore, it is impossible to discern whether RT was foregone or delayed for a clinically valid reason. Second, because these data are specific to North Carolina, our findings may not be generalizable to other states and settings. In particular, because our analysis required continuous enrollment in fee-for-service Medicare, our results may not be applicable to patients enrolled in health maintenance organizations or other insurance plans or to patients with more transient health insurance coverage. Third, geospatial methods and measurement of dis-
Distance to care are evolving sciences, and our approach may not be perfect. With more granular location data about patients and providers, analyses might reveal different or more complex relationships between distance to care and receipt of RT [56].

In summary, this study sought to understand geographic predictors of underuse of guideline-recommended RT among elderly breast cancer patients in North Carolina. Using a novel, population-based cancer data system—the Integrated Cancer Information and Surveillance System (ICISS), which is supported by the state of North Carolina through the University Cancer Research Fund—we found that distance to RT providers and rural-urban residence were important correlates of receipt of RT, controlling for all other factors, and that observed effects of distance to care were different in rural versus urban areas. These findings suggest that the subpopulations of breast cancer patients who are most vulnerable to underuse of life-prolonging therapies may need to be targeted for intervention and supported in creative ways to ensure their access to oncology care services.

### Acknowledgments
This work was supported by the Agency for Healthcare Research and Quality Comparative Effectiveness Research Career Development Award, 1-K-12 HS019468-01 (principal investigator, Weinberger; scholar, Wheeler), and by the Integrated Cancer Information and Surveillance System (ICISS), a UNC Lineberger Comprehensive Cancer Center resource funded by the state of North Carolina through the University Cancer Research Fund.

Potential conflicts of interest. All authors have no relevant conflicts of interest.

### References

### Table 4: Effects of Distance to Nearest Radiation Therapy (RT) Care Provider on Receipt of RT, by Rural-Urban Status

<table>
<thead>
<tr>
<th>Distance to care (reference group, less than 10 miles)</th>
<th>Urban dwellers (n = 1,276)</th>
<th>Rural dwellers (n = 662)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Odds ratio (95% CI)</td>
<td>Odds ratio (95% CI)</td>
</tr>
<tr>
<td>10–20 miles</td>
<td>0.87 (0.61–1.24)</td>
<td>1.73 (1.08–2.76)</td>
</tr>
<tr>
<td>Greater than 20 miles</td>
<td>0.54 (0.30–0.97)</td>
<td>1.09 (0.73–1.63)</td>
</tr>
</tbody>
</table>

Note. CI, confidence interval. These odds ratios and confidence intervals were computed using the SAS estimate statement in the generalizability estimating equations multivariable model presented in Table 3 (including the exact same covariates). To obtain the odds ratio of the interaction between distance to care of 10–20 miles (versus <10 miles) within urban areas, in the estimate statement we set the parameters to 1 for both 10–20 miles and the interaction term of “10–20 miles * urban area.”
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POLICY FORUM

Pushing Back Against the Long Shadow of Cancer

Introduction

In his Pulitzer Prize–winning book *The Emperor of All Maladies*, oncologist Siddhartha Mukherjee presents a “biography” of cancer. Mukherjee describes the complex and evolving interactions between environment, race, sex, and genes that not only cause our cells to mutate and turn on us but also thwart and confuse the scavenging cells that ought to clean of us the aberration. In his descriptions, Mukherjee humanizes cancer by fleshing out the “personality” of this disease that devours flesh and steals hope.

A diagnosis of cancer instills fear in patients, physicians, and those who are not directly affected by the disease. We look the other way. But the epidemiology of cancer is personal. Families share ominous genomes. Where we call home affects our survival. Our relatives, residence, sex, race, ethnicity, behaviors, and lifestyles all offer a murky and sinister prediction of cancer incidence and survival. Unfortunately, cancer is guilty of discrimination, as it disproportionately affects poor and minority individuals, and treatment options may be limited by availability, bias, and cost.

This issue of the NCMJ offers insights into how we employ drugs, data, and ingenuity to address cancer. This issue discusses various aspects of treatment, as well as prevention, response, and responsibility. While cancer remains the leading cause of death in North Carolina, this issue offers hope and promise. Screening, detection, and treatment are not our only options; prevention is also possible.

Even when cancer cannot be prevented, more and more of our neighbors, friends, family, and patients are living in remission from cancer or are living longer with cancer. Compassion for cancer survivors is paramount—both for those living with the disease and for those living with its memory. Finally, hospice and palliative care can offer relief for all who are affected by this disease. By restoring dignity, we can push back against the long shadow that cancer casts over both patients and families alike.

This issue inspires and renews our convictions. We too have biographies to be written.

Peter J. Morris, MD, MPH, MDiv
Editor in Chief
Cancer is the leading cause of death in North Carolina. This issue brief summarizes cancer statistics for the state; highlights important issues facing cancer patients, caregivers, providers, and policy makers; discusses the state's novel resources for cancer care research; and explores ways of managing this public health problem in order to improve outcomes for the people of North Carolina.

Cancer is an important public health problem in North Carolina. Articles in this issue of the NCMJ discuss ways of managing the problem and report on important cancer-related concerns facing the state's patients, caregivers, providers, and policy makers. The authors of these articles point out areas that warrant additional clinical resources, innovative reimbursement models, and research; they also highlight the rich cancer research activities in North Carolina and elucidate today's most salient oncology issues.

The State of the State, by the Numbers

More people in North Carolina die of cancer than of any other disease [1]. There were an estimated 56,164 cases of cancer in the state in 2013, which represents an increase in incidence of nearly 7% since 2007 [1]. Five types of cancer account for the vast majority of cases and cancer-related deaths in North Carolina: female breast cancer, cervical cancer, colorectal cancer, cancer of the lung or bronchus, and prostate cancer. Effectively implemented screening and prevention activities can reduce the burden of disease for all 5 of these types of cancers.

Cancer incidence and mortality vary substantially across the state. Figure 1 shows the age-adjusted average annual mortality rate from cancer of all types in North Carolina. According to data from the North Carolina Central Cancer Registry, the average annual age-adjusted mortality rate for the period 2003 through 2010 was as high as 243 cancer deaths per 100,000 population in some counties and as low as 148 deaths per 100,000 population in other counties (written communication from Anne-Marie Meyer, PhD, facilities director of the Integrated Cancer Information and Surveillance System; May 12, 2014). North Carolina's average annual cancer incidence rate for the years 2006 through 2010 was 471 new cases per 100,000 population, which was slightly higher than the US average of 454 cases per 100,000 [4]. Again, variations between counties were apparent, with annual incidence rates during that period ranging from 554 new cases per 100,000 population in Lenoir county to 386 new cases per 100,000 population in Bladen county [4]. Myriad factors likely contribute to differences in incidence rates across settings, including demographic characteristics of residents, health behaviors (eg, smoking, level of physical activity, consumption of vegetables and fruits), environmental exposures, genetic risk factors, and screening and prevention activities.

Two of the most commonly occurring types of cancer in the state are female breast cancer and cancer of the lung or bronchus. Average annual age-adjusted breast cancer mortality rates frequently have the highest poverty rates, as well; in many of these counties, more than 20% of the population lives in households with incomes below the federal poverty guidelines [2]. The commentary in this issue by Lea and King [3] discusses how regional poverty, lack of education, and other social determinants of health can lead to disparities in cancer mortality. Lea and King note that for the years 2006 through 2010, a 29-county region in Eastern North Carolina—which contains 15% of the state's population—had a substantially higher cancer mortality rate than did the state's other 71 counties. They also observe that African American patients in this 29-county area had a higher mortality rate than whites. Addressing these disparities must be a priority in the state, both for payers and for health systems. Research is needed to identify key barriers to the delivery of high-quality care in this region and to test and implement strategies—including novel and broader models of insurance coverage—that could narrow these disparities [3].

North Carolina's average annual cancer incidence rate for the years 2006 through 2010 was 471 new cases per 100,000 population, which was slightly higher than the US average of 454 cases per 100,000 [4]. Again, variations between counties were apparent, with annual incidence rates during that period ranging from 554 new cases per 100,000 population in Lenoir county to 386 new cases per 100,000 population in Bladen county [4]. Myriad factors likely contribute to differences in incidence rates across settings, including demographic characteristics of residents, health behaviors (eg, smoking, level of physical activity, consumption of vegetables and fruits), environmental exposures, genetic risk factors, and screening and prevention activities.

Two of the most commonly occurring types of cancer in the state are female breast cancer and cancer of the lung or bronchus. Average annual age-adjusted breast cancer mortality rates for the years 2003 through 2010 ranged from...
13 to 39 deaths per 100,000 population, with the highest rates found in counties in the eastern and far western parts of the state (see Figure 2). Based on data through 2009, the statewide average rate of mortality from breast cancer was 21.4 deaths per 100,000 population, which was similar to the national average of 22.2 deaths per 100,000 [1].

For cancer of the lung or bronchus, North Carolina’s average rate of mortality was 54.6 deaths per 100,000 population, based on data through 2009, which was higher than the national average of 48.5 deaths per 100,000 [1]. However, age-adjusted rates of mortality from cancer of the lung or bronchus vary widely across North Carolina counties, ranging from 39 deaths per 100,000 population to 81 deaths per 100,000 population (see Figure 3; online version only). Historically, the highest rates of death from cancer of the lung or bronchus have occurred in Scotland, Hoke, Caldwell, Swain, Jones, Lenoir, Granville, Gates, Currituck, and Rockingham counties [4]. In 8 of those 10 counties (all except Hoke and Lenoir), more than 20% of the adult residents were current smokers in 2010 [5].

Gynecologic cancers affect many women in the state, particularly those in underserved populations. Incidence and mortality trends for gynecologic cancers in North Carolina are described in this issue’s Running the Numbers column by Radhakrishnan and Rao [6]. The significant morbidity and mortality from gynecologic cancers emphasize the need to prioritize screening and prevention programs for cervical cancer, to develop referral networks and adequate insurance coverage, and to support patients who are diagnosed with cervical and other gynecologic cancers. Although rates of cervical cancer have decreased over time [4], the women who are still being afflicted by these cancers tend to be those who are most underserved. Cervical cancer could be largely eradicated through human papillomavirus (HPV) vaccination and screening during primary care visits, but substantial commitment will likely be required to ensure that the women who are most at risk for developing and dying from this disease have access to timely, effective, and affordable care.

Access to Care

Access to oncology care is problematic for many cancer patients in North Carolina, and lack of access to specialty care is a perennial concern, particularly for poor and rural patients. Development of referral networks and education of local providers about when referral is merited will improve quality of care in the state and reduce barriers to care. One such barrier is identified in an original article by S.B.W. and colleagues [7], which found that women who lived further from a radiation oncologist had lower rates of receiving recommended radiation therapy. This study suggests that supporting patients by offering transportation assistance or accommodations near treatment facilities may yield higher rates of compliance with therapies that are provided far from the patient’s home.

Cancer Screening and Prevention

With regard to receipt of cancer screening, North Carolina residents are doing quite well. A 2013 report indicated that the state’s rates of screening for cervical, colorectal, and prostate cancer are higher than corresponding national rates, and the state’s rate of screening for breast cancer is similar to the national average [1]. Unfortunately, the state is doing worse than the nation as a whole on certain metrics of cancer prevention, including fruit and vegetable consumption, time spent engaging in moderate or vigorous physical activity, and healthy body mass index (BMI) [1]. Relating to the promotion of cancer prevention behaviors, the commentary by Leeman and colleagues [8] describes methods for disseminating and implementing evidence-based interven-
tions. This commentary focuses on tobacco control as a case example, underlining the continued prevalence of smoking in the state and discussing the need for providers to use knowledge about cessation strategies in their practices.

Current controversies in cancer screening and the potential value of decision-making tools are described in the commentary by Miller and Reuland [9]. An ongoing challenge faced by health care providers and patients is how to have meaningful discussions about complicated and controversial issues in the brief time allotted for a clinical visit. Use of tools such as online videos that patients can watch in waiting rooms or counseling by nonclinical personnel might provide patients with the information they need without overtaxing office visits. A broader problem is that some clinicians and researchers have begun to question the value of certain types of screening. Screening for colon cancer and cervical cancer are still widely believed to be beneficial, but the benefits, costs, and potential harms of screening for lung, prostate, and breast cancer have recently been the focus of national debates [10].

For example, although lung cancer screening with computed tomography scans may be beneficial in high-risk smokers, the cost effectiveness of a national screening program to detect lung cancer is unclear. Resources may be better used to prevent smoking and to encourage quitting [10-13]. Similarly, prostate cancer screening using the prostate-specific antigen (PSA) test may have a very small benefit in men younger than 70 years, but it can also lead to adverse outcomes, such as unnecessary procedures. In older men, PSA testing is generally not beneficial, as it causes more harm than good. The US Preventive Services Task Force (USPSTF) concluded that harms can outweigh benefits for the average man, and the USPSTF now recommends against PSA testing [14].

Concerns have also been raised about breast cancer screening because of the results of the Canadian National Breast Screening Study, which found that mammography had no effect on mortality from breast cancer but did result in 1 overdiagnosed breast cancer for every 424 women screened [15]. Overall, however, the evidence and guidelines continue to support the use of mammography [16, 17]. These seemingly conflicting messages from various evidence-generating bodies understandably confuse and exasperate patients. Effective communication of evidence to lay audiences as well as clinical professionals is therefore critically important.

Racial Disparities

Racial disparities continue to plague North Carolinians. Compared with whites, African Americans in the state have higher incidence rates of the 5 main types of cancer and higher rates of mortality from those cancers [1]. In terms of cancer prevention, African Americans engage in physical activity less often than whites and have a higher average BMI; on the other hand, African Americans have lower rates of smoking among high school students and are more likely to undergo screening for breast and cervical cancer [1]. These data indicate significant room for improvement in cancer prevention, cancer detection, and receipt of effective and timely treatment among racial minorities in the state.

Effects of Cancer on Physical Health, Mental Health, and Financial Status

The physical and mental health issues faced by North Carolina’s cancer survivors are described in the commentaries by Naughton and Weaver [18] and Park and Rosenstein [19]. People with cancer face substantial burdens from symptoms, functional impairments related to their disease, and adverse sequelae of treatments. Even those who are cured or who experience prolonged survival with cancer often suffer substantial decrements in their quality of life,
which has widespread ramifications in terms of their psychological, social well-being and their ability to conduct daily activities and to participate in the workforce. The articles in this issue highlight the importance of understanding cancer survivors’ needs and developing programs that help survivors manage symptoms or provide support for survivors who are experiencing functional impairments or mental health problems. Use of dedicated patient navigators who have backgrounds in social work and/or nursing has been shown to improve symptom management, reduce use of emergency services, and improve quality of life [20-22]. Access to mental health services and support groups can also have positive effects on the patient experience and on the patient’s ability to participate in activities and work [23-25]. The use of screening tools to identify patients who need supportive care should thus be integrated into care.

Programs to improve coordination of care between cancer care specialists and primary care providers are necessary and may help to improve outcomes and reduce costs. For example, in the original article by Goyal and colleagues [26], the authors explore the role of patient-centered medical homes in potentially reducing health care utilization associated with chemotherapy-related adverse events among breast cancer patients. Their study found that Medicaid patients had significantly fewer inpatient admissions associated with chemotherapy-related adverse events if they were enrolled in Community Care of North Carolina (CCNC), which uses a medical-home model to provide care, than if they were not enrolled in CCNC. In the future, it is advisable to focus on developing resources such as patient-centered medical homes in a cost-effective manner, and there should be an emphasis on research that can measure their impact on quality of care.

Complementing these papers, the commentary by Dusetzina and colleagues [27] describes current issues regarding the cost of cancer care. As has been widely reported in the media, costs of cancer care are increasing for the system overall, as well as for individual patients (through higher out-of-pocket expenses). The commentary by Dusetzina and colleagues focuses specifically on drug costs, which have risen steadily. Another substantial component of health care costs is excessive treatment near the end of life, including potentially avoidable hospitalizations. Savings in this area can be facilitated by early use of palliative care services, which can yield improvements in symptoms and functioning, reduction in the number of hospitalizations, reduction in the use of toxic treatments near the end of life, improved quality of life, and decreased costs. These benefits are discussed in a commentary by Bull and Abernethy [28] and in a sidebar by Barfield [29]. Palliative care is not the same as hospice care or end-of-life care. It can be initiated early in the course of treatment for advanced or metastatic cancers and is largely supportive. Palliative care should be initiated by a palliative care specialist or a consulting team.

Private and public payers in North Carolina should provide reimbursement for early palliative care services, and hospital systems and practices should provide access to palliative care consultations for both inpatients and outpatients.

Special Issues in Cancer Research in North Carolina

North Carolina benefits from the presence of 3 institutions that are designated as comprehensive cancer centers by the National Cancer Institute (NCI): the UNC Lineberger Comprehensive Cancer Center at the University of North Carolina at Chapel Hill, the Duke Cancer Institute, and the Comprehensive Cancer Center of Wake Forest University. Additionally, through the NCI’s Community Clinical Oncology Program (CCOP) network, academic investigators and community physicians work together to design, conduct, and recruit patients (in particular, minority patients) to participate in important clinical trials. There are 3 active CCOPs across the state: Southeast Cancer Control Consortium CCOP, Wake Forest University CCOP, and SENC CCOP [30]. Howie and Peppercorn discuss ways of improving clinical research in their commentary, which describes ethical standards for conducting clinical research [31].

As strategies are developed for improving ethical standards in research and optimizing cancer outcomes, it will be increasingly important that researchers have timely data about the prevalence of disease, treatment patterns, outcomes, and insurance coverage among cancer patients. Meyer and colleagues [32] describe a powerful new research tool unique to North Carolina, the Integrated Cancer Information and Surveillance System (ICISS), which links claims-based data from public and private payers with the North Carolina Central Cancer Registry and other data sources. This resource, which is supported by the state’s University Cancer Research Fund, has already enabled myriad studies of quality of care and is anticipated to accelerate understanding of care patterns and treatment effectiveness. Moreover, this initiative is well ahead of what is being done in other states, and it thus provides an example of methods and approaches that can achieve complicated linkages of disparate data sources. ICISS also exemplifies the wealth of health care research activities in North Carolina, which have the potential to inform policy and improve quality of care in and beyond the state. Notably, ICISS data were used for both of the original articles featured in this issue [7, 26].

<table>
<thead>
<tr>
<th>FIGURE 3:</th>
<th>Age-Adjusted Average Annual Rate of Mortality From Cancer of the Lung or Bronchus in North Carolina Counties, 2003-2010</th>
</tr>
</thead>
<tbody>
<tr>
<td>This table is available in its entirety in the online edition of the NCMJ.</td>
<td></td>
</tr>
</tbody>
</table>
Conclusion

In summary, North Carolina has outstanding research activities and resources; nevertheless, it faces persistent challenges in ensuring broad access to high-quality affordable care and in closing gaps in outcomes related to geography, race, and poverty. Going forward, this wealth of research activities and capacity will hopefully be harnessed to inform the state’s policy initiatives, reimbursement models, intervention designs, and approaches to the delivery of care. NCMJ

Stephanie B. Wheeler, PhD, MPH, assistant professor, Department of Health Policy and Management, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill; faculty member, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill; research fellow, Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill; faculty team in cancer disparities, UNC Center for Health Promotion and Disease Prevention, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

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References

Controversies in Cancer Screening

David P. Miller Jr, Daniel S. Reuland

New studies raise concerns about whether screening for some cancers may cause more harm than good. This commentary reviews evidence relevant to current controversies in cancer screening, highlights why it is so difficult to formulate universal screening recommendations, and emphasizes the importance of informed and shared decision making.

Imagine that you are a physician attending a family reunion. Your long-lost cousins are fascinated to discover that you work in health care. Amid servings of barbecue and banana pudding, the conversation turns toward medicine. Francine, age 46 years, confides that she hates mammograms and wants to know whether she can postpone her next one for a few years. Doug, a 63-year-old mechanic without health insurance, casually mentions that he is considering attending a free prostate cancer screening event hosted by his local hospital. Judy, who is 58 years old and proud that she quit smoking last year, wonders whether she should get screened for lung cancer. You quickly realize that they want your advice on these topics. How would you respond?

These 3 scenarios highlight areas of recent controversy. Some well-respected clinicians will argue that all 3 individuals should receive cancer screenings immediately; others will argue that none should; and the majority likely will take positions somewhere in the middle. To understand the controversy, we need to understand the rationale for screening and the emerging evidence that raises questions about whether the balance of benefits and harms justifies screening in each scenario.

There is great enthusiasm for cancer screening in the United States. Widespread promotion of screening by the media, physicians, and advocacy groups has led to a predominant view that cancer screening is desirable in virtually all situations and that individuals have a moral obligation to receive screening. A 2004 national survey found that more than 40% of respondents believed that an 80-year-old woman who chooses not to have a screening mammogram is “irresponsible.” In addition, 73% of respondents said that they would rather receive a total-body computed tomography (CT) scan than $1,000 in cash [1].

This enthusiasm for screening is based on the premise that identifying disease in its early, asymptomatic state improves health outcomes by allowing for more effective treatments. Controlled trials have demonstrated that screening specific populations can reduce mortality for certain cancers. However, new evidence suggests that the benefits associated with cancer screening are often very small, and the potential harms are often overlooked [2, 3].

When making screening decisions, physicians and patients should balance the potential benefits of early treatment against the potential harms of false-positive results and unneeded treatments. This balance depends on many factors, including a person’s cancer-specific mortality risk, his or her life expectancy, and the likelihood that the screening test will find a cancer for which treatment is effective. Some cancers do not need to be detected and treated because they will never cause symptoms; researchers call detecting these inconsequential cancers “overdiagnosis.” On the other hand, some high-grade cancers arise between interval screenings and are so aggressive that treatment is ineffective.

Controversies in Prostate Cancer Screening

In 1992 the American Cancer Society (ACS) recommended annual prostate-specific antigen (PSA) testing for men beginning at age 50 years [4]. Prostate cancer is the most common type of cancer diagnosed in men, which would seem to support the benefit of screening [5]. However, prostate cancer is often indolent, and the majority of men older than 85 years have prostate cancer on autopsy [6]. Therefore screening is likely to detect many clinically insignificant tumors, which increases the chance of unnecessary treatment and limits the effectiveness of screening in reducing mortality. Indeed, 20 years after the ACS’s initial screening recommendation, recent evidence from 2 large trials [7, 8] suggests that screening asymptomatic men for prostate cancer has little to no effect on mortality.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial randomized more than 76,000 men aged 55–74 years to receive usual care or screening; the latter group received annual PSA testing for 6 years and annual digital rectal examination for 4 years. After 13 years, men in the screening group were 12% more likely to have been diagnosed with prostate cancer, but there was no signifi-
significant difference in the cumulative prostate cancer mortality rate (3.7 deaths per 10,000 person-years in the screening group versus 3.4 deaths per 10,000 person-years in the control group) [7]. However, approximately half of men in the control group received at least 1 PSA test, which may have diluted the observed effect of PSA screening.

The European Randomized Study of Screening for Prostate Cancer (ERSPC) randomized more than 162,000 men aged 55–69 years to receive PSA screening or no screening. In contrast to the PLCO trial, the ERSPC study observed a 21% reduction in the relative risk of death from prostate cancer after a median follow-up period of 11 years [8]. Despite this reduction in relative risk, screening resulted in an absolute reduction in prostate cancer mortality of only 0.1 deaths per 1,000 person-years, or 1.07 deaths per 1,000 men randomized. Translating this figure to a population, 1,000 men would need to be offered PSA screening for 10 years to avert 1 prostate cancer–related death.

On the other side of the equation, the potential harms of PSA screening are substantial. The ERSPC trial showed that 37 men will be diagnosed with prostate cancer for every death averted [9], leading to a large number of men undergoing unneeded treatment. Also, among those treated for prostate cancer, 20% to 40% will develop incontinence or erectile dysfunction [10] (Table 1). After reviewing the latest evidence in 2012, the US Preventive Services Task Force (USPSTF) concluded that these harms outweigh the potential benefits of PSA screening and reiterated its earlier recommendation against screening [10].

The ACS now recommends that health care providers inform men 50 years of age or older about the pros and cons of PSA screening so that patients can make an informed decision [5]. As additional years of follow-up accrue from the aforementioned trials, evidence regarding the benefits and harms of PSA screening may evolve, and recommendations may be changed. For now, it seems wise to simply inform men of the current evidence, which suggests that individual screening can answer that question. In our view, health care providers should not attempt to convince a woman to

### Controversies in Breast Cancer Screening

In November 2009, the USPSTF made headlines when it recommended against routine screening mammography for women younger than 50 years [11, 12]. Instead, the USPSTF emphasized that the decision to start screening before age 50 years should be made on an individual basis, taking into consideration each woman’s values regarding benefits and harms. However, not all groups agreed with the USPSTF recommendation. In reaction to the USPSTF’s recommendation, the ACS stated that it was continuing to recommend routine screening mammography starting at age 40 years [13].

Both the ACS and the USPSTF agreed that available evidence indicated that mammography screening reduces a woman’s relative risk of dying from breast cancer by approximately 15%, whether the screening is done when a woman is in her 40s or her 50s. However, because breast cancer is less common before age 50 years, an additional 565 women need to be screened to save 1 life when screening is performed for women in their 40s, compared with screening women in their 50s. In addition, delaying the start of screening until age 50 years would decrease the number of false-positive results by 60% while still averting 85% of preventable breast cancer deaths [14]. The USPSTF concluded that the marginal benefit of screening women before age 50 years did not clearly outweigh the additional anxiety and potential harms that would result from investigation of numerous false-positive results (Table 2). The ACS disagreed.

A study published in February 2014 adds to the controversy. The 25-year follow-up results of the Canadian National Breast Screening Study reconfirmed its earlier results that annual mammography in women aged 40–59 years did not reduce mortality from breast cancer beyond what was accomplished by a clinical breast examination and usual care [15]. Screening trials vary in the strength of their methodology, which can contribute to differences in findings, but the Canadian study was randomized at the patient level and was judged to have a low risk of bias by the latest Cochrane systematic review [16]. The Canadian study also found that 22% of invasive breast cancers detected by screening were overdiagnosed and hence overtreated [15], a finding that is consistent with those of other studies [17]. Like prostate cancer screening, breast cancer screening identifies many clinically insignificant tumors; perhaps as many as 10 patients are unnecessarily diagnosed and treated per death averted [18]. Although we lack reliable predictors to know which tumors represent overdiagnoses and which are “true saves,” there is an unsettling implication that the number of women who undergo unneeded treatments may be greater than the number who are helped by mammography.

Given the current data, what is the most appropriate recommendation? Only a fully informed woman who is considering screening can answer that question. In our view, health care providers should not attempt to convince a woman to

<table>
<thead>
<tr>
<th>TABLE 1. Expected Outcomes When 1,000 Men Aged 55–69 Years Are Screened With Prostate-Specific Antigen Testing Every 1–4 Years for 10 Years</th>
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<tbody>
<tr>
<td>100–120 men will have at least 1 false-positive result.</td>
</tr>
<tr>
<td>110 men will be diagnosed with prostate cancer.</td>
</tr>
<tr>
<td>29 men will develop erectile dysfunction as a result of treatment.</td>
</tr>
<tr>
<td>18 men will develop urinary incontinence as a result of treatment.</td>
</tr>
<tr>
<td>0–1 deaths from prostate cancer will be prevented.</td>
</tr>
</tbody>
</table>

Source: Adapted from the 2012 US Preventive Service Task Force recommendation statement [10].
receiving screening (or not to receive screening); rather, women should be informed about the nature and magnitude of the benefits and harms of screening mammography. Some women will review the statistics and not hesitate to start screening early, while others will find that the same statistics reassure them in their decision to delay screening. 

Controversies in Lung Cancer Screening

Results of the multicenter National Lung Screening Trial (NLST), which were published in 2011, show that screening using low-dose computed tomography (LDCT) reduces the risk of death due to lung cancer in high-risk individuals [19]. This was the first high-quality evidence that screening can reduce mortality from lung cancer, which is the leading cause of cancer-related death in the United States. Based on this evidence, the USPSTF [20] and other groups [21] issued new guidelines recommending that annual LDCT screening be offered to high-risk patients.

Despite its potential benefits, LDCT screening can also cause harms. In the NLST, 39% of screened individuals experienced at least 1 false-positive result after undergoing 3 scans, leading to costly and sometimes invasive procedures that did not find cancer [19, 21] (Table 3). Like screening for prostate and breast cancer, LDCT screening for lung cancer also likely leads to overdiagnosis and overtreatment of tumors that would never have affected patients. To prevent 1 lung cancer-related death, 320 people must be screened, which will result in 1.38 additional persons being diagnosed and treated unnecessarily [22].

In light of these data, it is reasonable to ask whether LDCT screening for lung cancer is appropriate for specific individuals. For example, consider Judy, the 58-year-old woman at the family reunion who smoked approximately 50 pack-years. In this case, she should be informed that the results of the NLST show that about 3 deaths from lung cancer will be prevented for every 1,000 individuals with a risk profile similar to hers who are screened annually. She should also be informed that for every 1,000 individuals screened, about 365 will experience at least 1 false-positive result during the first 3 rounds of screening, 25 of whom will have at least 1 invasive procedure, and 3 of these 25 individuals will experience a major complication [23]. Finally, she should know that 7.5% of all LDCT scans result in incidental findings [19], which could trigger additional workup that may or may not be beneficial.

However, if Judy smoked “only” 1 pack per day for 30 years, then her smoking history would be close to the minimum eligibility criteria for the NLST, and the chance that she would benefit from screening is considerably smaller. For participants in the NLST in the study’s lowest quintile of lung cancer risk, 5,276 persons had to be screened to avert 1 death during 6 years of follow-up, and more than 30% of these individuals had a false-positive result, with its attendant costs and risks [24].

The Need for Informed and Shared Decision Making

We have focused on screening for prostate, breast, and lung cancer because these are areas of recent controversy. Navigating this confusing sea of information is a challenge, particularly when a patient asks, “What would you do?” The challenge is great in part because patients and providers may not share the same values or preferences. People vary in their risk tolerance, their willingness to undergo procedures, and the degree to which they can make peace with uncertainty. Given this variety, it would be inappropriate to make a blanket recommendation for all patients.

We believe that the best approach is to ensure that patients are well informed about the potential benefits and harms of screening, so that they can make the best decisions for themselves. Unfortunately, patients often lack the knowledge to make decisions about screening. In surveys, patients have reported that health care providers almost always discuss the pros of screening but seldom discuss the cons [25, 26]. Therefore, it is not surprising that US adults overestimate both their risk of cancer and the benefits of screening [26]. Decision aids can help address these shortcomings by giving patients knowledge and a better understanding of their options [27]. Some relevant online decision aids are listed in Table 4 (online version only).

Changes are needed to ensure that patients and health care providers are well informed. Reimbursement policies should reward clinicians who take the time to inform patients of the intricate risks and benefits involved in the decisions

### Table 2
Expected Outcomes When 1,000 Women Aged 40–49 Years Are Screened Annually With Mammography for 10 Years

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Women</th>
</tr>
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<tbody>
<tr>
<td>510–690 women will have at least 1 false-positive result.</td>
<td>90</td>
</tr>
<tr>
<td>60–80 women will have a false-positive result that leads to a biopsy.</td>
<td>12</td>
</tr>
<tr>
<td>23 women will be diagnosed with breast cancer.</td>
<td>4</td>
</tr>
<tr>
<td>11 or fewer women will be overdiagnosed with breast cancer.</td>
<td>2</td>
</tr>
<tr>
<td>0.1–1.6 deaths from breast cancer will be prevented.</td>
<td>0.2</td>
</tr>
</tbody>
</table>

Source: Adapted from Welch and Passow [18].

### Table 3
Observed Outcomes After 6.5 Years of Follow-Up, per 1,000 Participants, Among Individuals Who Underwent 3 Annual Screenings with Low-Dose Computed Tomography

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Number of Participants</th>
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<tbody>
<tr>
<td>365 participants had at least 1 false-positive result.</td>
<td>365</td>
</tr>
<tr>
<td>25 participants had a false-positive result leading to an invasive procedure.</td>
<td>25</td>
</tr>
<tr>
<td>3 participants with a false-positive result experienced a major complication of a procedure.</td>
<td>3</td>
</tr>
<tr>
<td>3–5 participants were overdiagnosed with lung cancer.</td>
<td>3–5</td>
</tr>
<tr>
<td>Approximately 3 deaths from lung cancer were prevented.</td>
<td>3</td>
</tr>
</tbody>
</table>

Source: Data are from the National Lung Screening Trial Research Team [19] and Patz et al [22].
they face. Screening trials should measure not only benefits but also harms, which have rarely been tracked in the past [3]. Researchers at the University of North Carolina at Chapel Hill are currently examining how potential harms are addressed in screening decisions and policy (http://smart-screening.org). We should also be wary of observational studies, which are prone to length and lead-time biases, and we should remain open to newer evidence showing that the net benefits of screening for some cancers are substantially smaller than we previously thought. Although medical knowledge is continually growing and changing, focusing on fully informing ourselves and our patients will always be helpful. NCMJ

David P. Miller Jr, MD, MS associate professor, Internal Medicine and Public Health Sciences, Wake Forest School of Medicine, Winston-Salem, North Carolina.

Daniel S. Reuland, MD, MPH associate professor, Division of General Medicine and Clinical Epidemiology, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

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References
Recent regulatory and policy changes may help to improve the affordability of some high-cost cancer treatments. However, larger systemic changes are needed to address the excessive growth in spending for cancer therapies and to ensure that patients and payers receive maximum value for their health care dollars.

The National Institutes of Health estimated that the annual cost of cancer in the United States was more than $216 billion in 2009, including $86.6 billion in direct medical costs [1]. Although recent evidence suggests that the historic growth in pharmaceutical spending in the United States has slowed, spending on specialty pharmaceutical products—including most new cancer treatments—continues to grow rapidly. In fact, all of the cancer therapies approved by the US Food and Drug Administration (FDA) between 2010 and 2013 were priced at more than $5,000 for a month of treatment, and 43% were priced at more than $10,000 for a month of treatment [2]. Unfortunately, the costs of treatment to insurers and patients do not always reflect the value of these treatments.

In September 2013, in a report titled Delivering High-Quality Cancer Care [3], the Institute of Medicine of the National Academies directly addressed the importance of making high-quality cancer care accessible and affordable for patients and for the health care system. One of the report’s key recommendations is that new payment models and insurance benefit designs are needed to enable patients to take an active role in choosing therapies that align with their needs, values, and preferences [3]. In this commentary, we evaluate the affordability of cancer treatments from the perspective of the health care system and from the perspective of the patient. For each of these 2 perspectives, we discuss the key obstacles that must be overcome to improve affordability and to support value.

Making Treatments More Affordable to the Health Care System

It is widely known that pharmaceutical prices are higher in the United States than in other developed countries, but reliable information regarding the price of medications is difficult to find. This price often depends on negotiations between payers and manufacturers or between pharmacy benefit managers and manufacturers. In addition, the estimated costs of developing a pharmaceutical product are not made public and likely vary widely, making it impossible to ascertain whether the price of a drug is set to offset the actual costs of development or if the price is set as high as the market will bear. Illustrating the elasticity of drug pricing, the colon cancer drug ziv-aflibercept (Zaltrap, Sanofi/Regeneron Pharmaceuticals) was originally priced at nearly $11,000 per month. In the fall of 2012, however, Memorial Sloan Kettering Cancer Center publicly announced their refusal to pay for ziv-aflibercept, because it was twice as expensive but no more effective than bevacizumab (Avastin, Genentech), another drug that is used for the same purpose [4]. In response to the ensuing public outcry, the manufacturer of ziv-aflibercept began offering a 50% discount on the drug’s original price [5].

Another difficulty in making oncology medications more affordable is the threat of generic competition. For most cancer therapies, it is assumed that a generic version will enter the market when the drug’s patent expires, so drug manufacturers act to maximize their profits during the early years of patent exclusivity. This has resulted in very high prices for cancer therapies that are new to the market. For example, 11 of the 12 oral cancer drugs approved by the FDA in 2012 cost more than $100,000 per year [6].

Another difficulty is that many new chemotherapeutics are biologic drugs. Unlike small-molecule, chemically synthesized drugs, biologic cancer therapies have often faced no competition, even after their patent expires, because historically there was no path for the development of generic biologics. This lack of competition reduced the incentive for companies to lower prices. Fortunately, the Biologics Price Competition and Innovation Act of 2009 (which was part of the Patient Protection and Affordable Care Act of 2010) [7] set in motion a regulatory process for approval of “generic” biologic medications (biosimilars). In order to gain FDA approval, the manufacturer must demonstrate that the biosimilar product is highly similar to the approved biologic. Although this is a positive step for reducing the cost of bio-
logics, these therapies may pose special challenges because of the complexity both of the products themselves and of the manufacturing process [8]. If manufacturers are required to replicate clinical trial data to prove biosimilarity, the magnitude of savings generated from traditional generic medications likely will not be realized in this market.

Perhaps one of the most significant obstacles to making cancer treatments more affordable is the inability of public insurers (primarily Medicare) to negotiate for lower drug prices [9]. For example, in the Medicare Prescription Drug, Improvement, and Modernization Act of 2003, Medicare was explicitly prohibited from negotiating pharmaceutical prices for Medicare Part D prescription drug plans [10]. Moreover, anticancer therapies are considered a protected class under Medicare Part D, meaning that plans must cover all therapies in the class. Manufacturers thus have little incentive to reduce prices in order to be included in formulary lists. Although these rules were established to protect patients’ access to therapies, a consequence has been less competition on price within the protected categories.

Making Treatments More Affordable to Patients

Historically, chemotherapy was largely obtained via infusion in physician offices and clinics, where patients often paid only an outpatient visit copayment; there was usually no additional fee for the infused drug itself [11, 12]. However, the landscape for cancer pharmacotherapy is changing. Since 2000, approximately 40% of new cancer drugs approved by the FDA have been oral therapies [13]. Research suggests that patients prefer oral therapies to infused therapies due to the ease of administration [14, 15]. However, oral cancer therapies can be extremely expensive for patients, because they are reimbursed through a patient’s pharmacy benefits rather than through his or her medical benefits. Depending on the structure of their pharmacy benefits, patients often face high cost sharing, including high copayments or coinsurance requirements [16, 17]. Medicare beneficiaries may be particularly vulnerable to high cost sharing for prescription medications, because Medicare Part D includes most oral oncologics in its specialty tier, and many plans require that patients pay 33% of the cost of these drugs [18].

High out-of-pocket costs have been cited as one possible reason for inadequate use of oral cancer therapies [19, 20]. For example, chronic myeloid leukemia is a condition for which even small lapses in adherence are associated with poor outcomes. A recently published study coauthored by S.B.D. [19] found significant variation among privately insured patients in out-of-pocket expenditures for a 30-day supply of therapy. Costs to patients ranged from $0 to more than $4,000, with 6.5% of privately insured patients paying more than $500 for a single prescription refill, or more than $6,000 yearly. Further, higher copayments were associated with a 70% increase in the risk of discontinuing therapy and a 42% increase in the risk of having inadequate adherence to therapy during the first 6 months of treatment [19]. High cost sharing for oral oncology drugs is also associated with abandonment of new prescriptions at the pharmacy; one study found that the odds of abandoning a prescription were more than 4 times greater for patients paying more than $500 in out-of-pocket costs compared with those paying $100 or less [21]. Clearly, therapeutic benefit will only be gained if a patient is able to access the therapy and take it as required.

Policy Changes That May Improve the Affordability of Oral Cancer Drugs

There are several important changes under way that may improve the affordability of prescription medications. First, the Affordable Care Act places limits on out-of-pocket costs for patients enrolled in private health insurance plans, and spending on prescription medications is included when calculating those costs; for 2014, the out-of-pocket maximums are $6,350 for an individual and $12,700 for a family [22]. Historically, prescription medications were excluded from these maximums, exposing patients to unlimited pharmaceutical spending. However, premiums are not included in these out-of-pocket calculations, and the maximum limits do not apply to "grandfathered" health plans. Further, patients whose pharmacy and medical benefits are administered by different companies will not benefit from the cap until at least 2015, while plans work out processes for calculating these patients’ out-of-pocket maximums [22].

Another part of the Affordable Care Act addresses the Medicare Part D coverage gap known as the “doughnut hole.” In 2014, Medicare beneficiaries are required to pay 47.5% of the branded drug price during the coverage gap in their Part D drug plans; this amount is set to decrease over the next several years, and patient cost sharing will be reduced to 25% of the branded drug price by 2020 [23]. However, it should be noted that branded oral cancer therapies can cost nearly $10,000 per month, so patients may face substantial cost sharing even after they reach the catastrophic phase of coverage.

By early 2014, 28 states and the District of Columbia had passed parity laws for oral cancer drugs, which ensure that patients pay no more for oral cancer therapies than they pay for intravenous therapies offered by the same health plan. Currently, the legislation applies only to patients living in states that have passed such laws who have health insurance that is purchased by their employer from an insurance company (ie, fully insured health plans). Discussions about such parity laws are currently under way in North Carolina. In May 2013, the North Carolina House of Representatives amended House Bill 609, the North Carolina Cancer Treatment Fairness Act, to cap patients’ monthly out-of-pocket expenses for oral chemotherapy at $300 per prescription. This legislation is currently awaiting consideration by the North Carolina Senate [24].
On a national level, the Cancer Drug Coverage Parity Act of 2013 was introduced in the US House of Representatives in April 2013 [25], and the Cancer Treatment Parity Act of 2013 was introduced in the US Senate in December 2013 [26]. If enacted, these bills would standardize coverage across states by mandating parity for oral cancer therapies covered by privately insured health plans in the United States, including plans covered by the Employee Retirement Income Security Act. Notably, none of the existing or pending parity legislation applies to Medicare or Medicaid, which are the largest payers for cancer health services in the United States.

Alternative Strategies for Improving the Affordability of Cancer Drugs

There have been major advances in cancer pharmacotherapy—including the development of several targeted therapies that have revolutionized the treatment of specific cancers—but many therapies still provide only minor gains in life expectancy. This is particularly true for the many cancer therapies that are approved to treat metastatic and/or late-stage cancers, where curative intent is no longer the goal. In this setting, pricing appears to be unrelated to actual benefits gained [27], because many very expensive treatments extend life by only a few weeks. For example, regorafenib (Stivarga, Bayer HealthCare) is an oral chemotherapy agent that was recently approved for treatment of metastatic colorectal cancer; this drug prolongs survival by only 1.4 months compared with placebo (6.4 months versus 5.0 months) [28], and it costs nearly $10,000 per month [29].

Understanding the extent to which high-cost treatments affect patients’ quality of life is important for evaluating their value to patients and to society. From the patient perspective, these costs can represent considerable financial hardships for themselves and their families, including bankruptcy [30–32]. From the system-level perspective, creative solutions include the adoption of value-based pricing and the use of “meaningful clinical benefit” thresholds to establish fair pricing of treatments [33, 34]. However, such strategies remain challenging to implement due to public pressure and concerns about health care rationing. Moreover, there is evidence that many patients with metastatic cancers value high-cost specialty medications and continued treatment, even when those therapies offer limited benefits [35, 36]. This situation can create tension between patients, who often want continued treatment for incurable diseases, and payers, who must determine which therapies to cover and how generously to reimburse these products.

In summary, there is widespread agreement that the trajectory for health care spending in the United States is unsustainable; however, there is a resistance to restricting coverage for cancer-related treatments. Recent policy changes may help to improve the affordability of some high-cost drugs, but the costs still remain too high for many patients. Despite the appeal of value-based insurance designs, such efforts have met with strong resistance in the United States. Payers have been reluctant to place restrictions on any cancer treatments, but not prioritizing coverage for the most effective therapies may result in increased costs for all therapies. Thus we need to better understand the value of high-cost drugs and to assess whether value-based insurance designs could improve affordability and access to the drugs that are most likely to benefit patients.

Stacie B. Dusetzina, PhD assistant professor of medicine, Division of General Medicine and Clinical Epidemiology, UNC School of Medicine; assistant professor of public health, Department of Health Policy and Management, UNC Gillings School of Global Public Health; member of the UNC Lineberger Comprehensive Cancer Center; research fellow, Cecil G. Sheps Center for Health Services Research, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Benyam Muluneh, PharmD clinical pharmacist practitioner, Department of Hematology/Oncology and Department of Pharmacy, UNC Health Care; adjunct assistant professor, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Tippu Khan, PharmD assistant professor, UNC Eshelman School of Pharmacy, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Kristy L. Richards, PhD, MD member of the UNC Lineberger Comprehensive Cancer Center; assistant professor of medicine and genetics, Division of Hematology/Oncology, UNC School of Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Nancy L. Keating, MD, MPH associate professor of medicine, Department of Health Care Policy, Harvard Medical School; associate physician, Division of General Internal Medicine, Brigham and Women’s Hospital, Boston, Massachusetts.

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Despite the growing menu of evidence-based interventions to prevent and control cancer, such interventions continue to be underused in practice. This commentary describes interactive approaches to speeding the dissemination and implementation of evidence-based interventions and illustrates these approaches using examples from obesity prevention and tobacco control.

Cancer is the leading cause of death in North Carolina, with mortality rates higher than the national average [1]. Rates of tobacco use, physical inactivity, and obesity are also higher in North Carolina than in the country as a whole [1], which further contributes to cancer risk [2]. The National Institutes of Health (NIH), the Centers for Disease Control and Prevention (CDC), and other groups have invested extensively in developing and testing interventions to reduce cancer risk and to improve cancer detection and treatment. With this funding, researchers have developed effective interventions to increase rates of cancer screening, to facilitate treatment decision making, and to help patients stop smoking [3, 4]. Researchers also are identifying ways to create environments that support healthy choices and thereby reduce cancer risk; for example, implementing smoke-free policies at work sites can reduce tobacco use and exposure to secondhand smoke [5]. As a result, clinicians and public health practitioners now have access to a growing menu of evidence-based interventions (EBIs).

However, EBIs continue to be underused [6-8]. According to one estimate, it takes an average of 17 years for just 14% of research to transfer to practice [9]. Thus a central challenge in preventing and controlling cancer is identifying better ways to speed the dissemination and implementation of EBIs into practice. A recent NIH funding opportunity announcement defined dissemination as “the targeted distribution of information and intervention materials to a specific public health or clinical practice audience,” and it defined implementation as “the use of strategies to adopt and integrate evidence-based health interventions and change practice patterns within specific settings” [10].

Historically, the translation of research to practice has been a linear process, with researchers generating findings, translating them for use, and then disseminating them to nurses, physicians, health educators, administrators, and other public health and clinical practitioners who individually and collectively implement EBIs [11]. Given the unidirectional nature of this process, researchers’ priorities have driven the development and dissemination of interventions, and less attention has been given to the needs and priorities of practitioners [12]. As a result, many EBIs are either irrelevant or too complex and costly to apply within the constraints of current practice environments [13]. Even when EBIs are relevant and feasible, they are often disseminated in formats that provide little guidance on how to adapt them to different contexts and/or how to integrate them into practice [13, 14]. Also, by the time EBIs are disseminated effectively, they may no longer be congruent with practitioners’ priorities and resources.

In recent years, there has been growing recognition that transferring EBIs into practice is more successful when the flow of information is bidirectional, with researchers and practitioners interacting to develop, disseminate, and implement EBIs. In this commentary, we will apply the Interactive Systems Framework for dissemination and implementation [15] to describe interactive approaches that can be used to transfer EBIs into practice. Because high rates of tobacco use, physical inactivity, and obesity are among the reasons why cancer is the leading cause of death in North Carolina, we will use examples from obesity prevention and tobacco control to illustrate these approaches.

The Interactive Systems Framework posits that the successful dissemination and implementation of EBIs requires interaction among 3 types of systems: synthesis and translation systems, which disseminate EBIs; delivery systems (eg, practitioners), which implement EBIs; and support systems, which build the capacity of delivery systems to adopt and implement EBIs within specific settings [15]. Examples of each of these 3 types of systems can be found in Figure 1.

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Address correspondence to Dr. Jennifer Leeman, School of Nursing, University of North Carolina at Chapel Hill, CB #7460, Chapel Hill, NC 27599 (jleeman@email.unc.edu).
Interaction at the Level of Synthesis and Translation Systems

Table 1 lists some of the organizations that synthesize and translate EBIs for practitioners working in cancer prevention and control. The US Preventive Services Task Force and the Guide to Community Preventive Services conduct systematic reviews of the literature to identify interventions that have worked across multiple research studies. This approach yields EBIs with the strongest evidence in support of their effectiveness [16], but it provides minimal guidance on how to implement these EBIs. The National Cancer Institute takes a different approach and identifies Research-Tested Intervention Programs (RTIPs), which are specific interventions whose efficacy has been demonstrated by one or more reasonably well-designed research studies. The RTIP interventions are translated into a format that provides detailed guidance and materials to support implementation [17]. This process yields a “packaged” intervention that is intended to be ready for adoption and implementation in practice.

Despite the extensive resources invested in synthesis and translation of EBIs, public health and clinical practitioners have been slow to adopt and implement EBIs [7, 18]. Practitioners are often overwhelmed by the number of EBIs and may lack the information and guidance needed to use them in practice [19-21]. In response, synthesis translation systems are partnering with practitioners to translate EBIs into formats that better address practitioners’ needs and priorities.

For example, researchers and staff at the Center for Training and Research Translation (Center TRT), which is based in the Center for Health Promotion and Disease Prevention at the University of North Carolina at Chapel Hill (UNC–CH), have conducted numerous interviews and surveys to understand the needs and preferences of public health practitioners working in obesity prevention. Center TRT staff members then translate EBIs into a template that provides the information that practitioners say they need to adopt and implement interventions in practice [21, 22]. Furthermore, many of the interventions that Center TRT disseminates were developed and evaluated by public health practitioners rather than by researchers. These practice-based interventions all employ recommended EBI strategies, such as those recommended by the Community Guide, and they provide guidance that is based on practitioners’ real-world experience implementing the strategies [23]. The Center TRT template includes a summary of the evidence in support of the intervention, details on the steps required to implement the intervention, and links to materials and tools that practitioners can use to implement it and to evaluate processes and outcomes. Center TRT disseminates intervention templates via its Web site (www.centertrt.org), which is accessed by more than 22,000 unique visitors annually.

In another example of a synthesis and translation system partnering with practitioners, researchers at East Carolina University (ECU), UNC–CH, and Appalachian State University in 2011–2012 interviewed county managers, mayors, planning staff, and other local leaders from eastern and western North Carolina to discover how these individuals viewed the adoption of CDC-recommended environmental and policy-change EBIs [24]. The researchers found that rural leaders rated EBIs as more feasible and acceptable when the EBIs created opportunity and choice (eg, improving access to outdoor recreational facilities), and they rated EBIs as less feasible and acceptable when they were more restrictive and regulatory (eg, limiting advertisement of unhealthy foods and beverages) [25]. The same research team is currently working to translate the CDC’s recommended EBIs for use in rural areas, with the goals of reducing disparities among North Carolina residents and preventing obesity, cancer, and other chronic conditions. Taken together, these

### Table 1
Selected Organizations That Synthesize and Translate Cancer-Related Evidence-Based Interventions

- The Cochrane Collaboration ([http://www.cochrane.org](http://www.cochrane.org))
- Center for Training and Research Translation ([http://www.centertrt.org](http://www.centertrt.org))
- Counter Tobacco ([http://countertobacco.org](http://countertobacco.org))
partnerships between researchers and practitioners illustrate the potential benefits of an interactive approach to synthesizing, translating, and disseminating EBIs.

Interaction Between Delivery Systems and Support Systems

Although the Internet is an effective channel for disseminating EBIs, posting interventions online is generally insufficient to promote their adoption and implementation. The Interactive Systems Framework posits that health care providers and health care delivery systems require additional support to select the EBIs that best fit their needs and to adapt and implement these EBIs in their practice settings [26]. Thus researchers and staff members at universities across the country are functioning as “support systems” and partnering with providers and communities to build their capacity to implement EBIs.

Researchers take a variety of approaches to supporting providers. These interactions range from engaging in participatory partnerships to providing training, technical assistance, and tools. An example of a participatory approach is the partnership between the North Carolina Department of Health and Human Services (DHHS) and researchers from ECU and UNC-CH. Within this CDC-funded partnership, researchers are enhancing DHHS’s capacity to evaluate EBIs that aim to increase access to farmers’ markets—a goal identified in the CDC’s list of recommended policy and environmental strategies [24]. With support from DHHS, local communities are increasing access to farmers’ markets through promotional activities, Supplemental Nutrition Assistance Program (SNAP) Electronic Benefit Transfer systems, and new zoning ordinances. The researchers and DHHS are then evaluating the impact of farmers’ markets on the fruit and vegetable consumption of North Carolina residents [27].

At the other end of the engagement continuum, UNC-CH researchers—working in collaboration with the Center for Public Health Quality, the Center for Healthy North Carolina, and the North Carolina Institute of Public Health—are training public health practitioners in the use of EBIs. The 2-day training program provides guidance on how to engage partners, select EBIs, adapt and implement EBIs in practice, and evaluate processes and outcomes. In addition to training, support systems often provide tools that encourage adoption and implementation of EBIs in local settings. Such tools can include any electronic or print resources that practitioners could use to plan, implement, or evaluate an intervention.

Examples of tools created by researchers at UNC-CH include those disseminated by CounterTobacco.org, a CDC-funded Web-based resource, and Counter Tools, a nonprofit organization, both of which were developed to boost practitioners’ capacity to counter tobacco marketing in retail environments such as gas stations, pharmacies, and corner stores. Marketing tobacco in these locations creates an environment that prompts initiation of tobacco use and interferes with quit attempts [28]. In addition to translating and disseminating EBIs, CounterTobacco.org disseminates toolkits for engaging youth and galleries of photos and other media that can be used to raise awareness and to engage partners. Counter Tools provides enhanced technical assistance and disseminates both the Store Audit Center, a mobile data-collection system that public health and other community-based practitioners can use to document individual retailer environments, and the Store Mapper, an interactive mapping Web site that allows providers to find and display the locations of tobacco retailers and to calculate geospatial data needed for local decision making (eg, retailer density, correlations between density and race or poverty, and the population reach of policy solutions). These examples represent novel approaches through which support systems can boost the ability of delivery systems to implement EBIs.

Increased use of EBIs is essential to reducing cancer morbidity and mortality. EBIs are most likely to be relevant and usable when researchers and practitioners work together on their development, dissemination, and implementation. Thus synthesis and translation systems benefit from inquiries into practitioners’ priorities, constraints, and preferences as they relate to EBIs and the ways they are disseminated. In addition, support systems (eg, university researchers and staff) should interact with delivery systems to build their capacity to use EBIs; those interactions can range from participatory partnerships to the provision of training, technical assistance, and tools. Researchers at ECU and UNC-CH are interacting with public health organizations and health care providers across the state to find innovative ways of efficiently and effectively bringing EBIs for cancer prevention and control to the people of North Carolina.

Jennifer Leeman, DrPH, MDiv assistant professor, School of Nursing, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. Stephanie Jilcott-Pitts, PhD associate professor, Department of Public Health, Brody School of Medicine, East Carolina University, Greenville, North Carolina. Allison Myers, MPH deputy director, Counter Tobacco, Department of Health Behavior, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.
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The Integrated Cancer Information and Surveillance System (ICISS) facilitates population-based cancer research by developing extensive information technology systems that can link and manage large data sets. Taking an interdisciplinary “team science” approach, ICISS has developed data, systems, and methods that allow researchers to better leverage the power of big data to improve population health.

Advances in information technology and data computing have revolutionized population-based research by providing access to large quantities of secondary data; these linked databases are sometimes referred to as “big data” [1]. Using these data for public health research or clinical research requires that researchers broaden their horizons beyond the traditional surveillance model, as working with big data is very different than analyzing narrowly focused, treatment-oriented clinical trial data. Big data must be carefully and effectively leveraged if it is to accurately reflect the heterogeneous populations it represents. This effort requires an agile research environment that quickly adopts advances in computing technology to continually integrate data while applying novel methods to untangle their complexity.

North Carolina’s Integrated Cancer Information and Surveillance System (ICISS) is a novel research data system enabled by unprecedented support from the North Carolina General Assembly through the University Cancer Research Fund [2]. ICISS employs an interdisciplinary “team science” approach that requires the close collaboration of researchers from many fields, including clinical and population sciences, as well as unparalleled partnerships with computer science and health informatics professionals [3]. Integrating and operationalizing these data requires significant investments in a secure, high-level, data-computing and research infrastructure that is nimble enough to address longitudinal data needs and can adapt rapidly to evolving research methods.

The mission of ICISS is to improve cancer outcomes in North Carolina by assembling, linking, and harmonizing big data to facilitate high-impact, cancer-focused research spanning the cancer continuum [4]. This goal is accomplished through integrated activities relating to data sets, systems, and methods (see Figure 1).

First, ICISS develops and maintains an innovative, comprehensive, and prospectively linked library of large population-based data sets that include measures across the cancer care continuum, from screening to postdiagnosis outcomes. Second, ICISS includes a secure virtual computing platform and a software development team, which together deliver innovative research tools and meet technical needs. Integrated into daily work flows, these tools enable navigation of clinical coding catalogs, cohort discovery, project tracking, and knowledge retention. Third, ICISS facilitates cutting-edge cancer outcomes research by cultivating an interdisciplinary team environment and by applying novel data management and analytic methods for studying large sets of nonexperimental data. Many aspects of the ICISS system, including its unique coding search, tracking tools, and methods expertise, are publicly accessible to North Carolina cancer researchers at http://iciss.unc.edu.

ICISS Governance and Data Security

A tightly managed set of governance policies and procedures helps to ensure that use of ICISS resources aligns with the research missions of ICISS and of the University Cancer Research Fund, and that use of these resources is in compliance with numerous security safeguards and regulatory requirements. The governance process is overseen by a multidisciplinary steering committee of researchers who represent several schools within the University of North Carolina (UNC) and various data partners, including the North Carolina Central Cancer Registry (NCCCR). This oversight spans all steps of the research process, from an initial letter proposing a research study using the ICISS data, to security training and oversight of projects, to prepublication review of research products. The UNC Institutional Review Board (IRB) oversees protocols for maintaining and linking ICISS data as a resource, as well as for each research study that uses ICISS data. In addition, a global security management
plan preserves the confidentiality, integrity, and availability of personally identifiable information and protected health information, including limited data sets. This security plan ensures regulatory compliance with the Health Insurance Portability and Accountability Act of 1996 (HIPAA), the Federal Information Security Management Act of 2002, and North Carolina’s state law regarding data security breaches.

ICISS Data

The integrated ICISS research data have given North Carolina a unique ability to perform sophisticated analyses in multiple, diverse research areas including comparative effectiveness, health disparities, quality improvement, patient-centered outcomes research, public health services and systems research, implementation science, epidemiologic and biostatistical methods, health information technology, health economics, and organizational studies. The data incorporate numerous measures on multiple levels and characterize a wide range of influential factors, including personal characteristics and behaviors, health care organizational factors, and broader environmental influences (see Figure 2). These measures span the cancer continuum from risk and genetic predisposition through diagnosis, treatment, intermediate outcomes, and end-of-life care.

**Person-level data.** Person-level data are drawn from numerous sources, including the NCCCR, Medicare, Medicaid, and private health insurance plans. When linked, these combined data can richly characterize all North Carolinians with cancer, as well as those without cancer, for the years 2003 through 2010. NCCCR data provide detailed information about the cancer diagnosis such as tumor size, aggressiveness, and extent of disease; basic demographic information; the date of diagnosis; vital status; and the date of death. Administrative and insurance claims data characterize the health characteristics and health care utilization of cancer and noncancer patients, which is important for several reasons, including understanding of cancer prevention and early detection.

Cases are linked to multipayer claims data sets through deterministic and probabilistic linkage methods. Together these data sets cover approximately 5.5 million unique individuals—about 55% of the state’s overall population and about 70% of the cancer patients in North Carolina. Claims files provide information on diagnoses, procedures, and dates of service, and they allow researchers to observe patients before and during diagnosis, through treatment, and during continued follow-up. Treatment morbidity (e.g., toxicities) and comorbidities can be observed for as long as the patient maintains insurance coverage and receives billable health services. Mortality and date of death are captured within the NCCCR data and can often be verified using the claims enrollment files. The data are updated regularly as more information becomes available from relevant data partners.

**Provider-level data.** Extensive research has demonstrated the influence of health care provider characteristics on cancer diagnosis, treatment, and outcomes. ICISS data include information from the North Carolina Health Professions Data System (managed by UNC’s Cecil G. Sheps Center for Health Services Research) [7], the American Medical Association, and the American Hospital Association, and this information can be linked to claims data. ICISS also has geocoded data from the North Carolina Health Professions Data System (2000–2010), which allows researchers to examine the impact of distance to care and other access issues [8-10].
All provider data are managed centrally within ICISS and are thoroughly deidentified after linkage, so identifying data are not released to research teams.

**Area-level data.** Area-level data sets can be linked at multiple geographic levels to characterize environmental, socioeconomic, and political contexts [11, 12]. These data sets include Area Health Resources Files from the Health Resources and Services Administration [13], the Robert Wood Johnson Foundation’s County Health Rankings [14], the National Profile of Local Health Departments compiled by the National Association of County and City Health Officials [15], the Behavioral Risk Factor Surveillance System of the Centers for Disease Control and Prevention, and US Census tract data from the American Community Survey. Together these data include thousands of variables that contextualize North Carolina counties and local health departments.

**Reference data.** The usability of observational data is contingent on the successful interpretation and use of coded data. For example, linking and using ICISS data require knowledge of US Census data; name(s) data; codes for medical diagnoses, procedures, and drugs; and crosswalks between codes, including city, ZIP, census, and county codes. ICISS has developed a unique Web-based reference search system that allows for high-validity, efficient code identification, definition, and crosswalk.

The ICISS clinical coding tool systematically normalizes and links various nomenclatures through multiple crosswalks; these nomenclatures include the 9th and 10th revisions of the International Classification of Diseases (ICD-9 and ICD-10); the International Classification of Diseases for Oncology (ICD-O); Current Procedural Terminology (CPT); Healthcare Common Procedure Coding System (HCPCS); Systematized Nomenclature of Medicine—Clinical Terms (SNOMED CT); National Drug Codes (NDC); Anatomical Therapeutic Chemical (ATC) Classification System; and Logical Observation Identifiers Names and Codes (LOINC).

**ICISS Systems**

Systems infrastructure—the second core element of ICISS—is aligned to support the entire research project life cycle while ensuring the security and privacy of ICISS data.

**Aggregated data environment.** An online platform for querying deidentified, aggregated data is designed to help investigators perform preliminary data review through tailored views of ICISS data. Variables such as cancer site, age, sex, and ethnicity can be overlaid with census data, health indicators, and socioeconomic variables to assess basic

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**FIGURE 2.**
Integrated Cancer Information and Surveillance System Data

- **Sources of data on environmental, socioeconomic, or political context**
  - US Census
  - Robert Wood Johnson Foundation County Health Rankings
  - CDC Community Health Indicators
  - Area Health Resources Files
  - Environmental monitoring programs

- **Sources of data on health care resource characteristics**
  - North Carolina Health Professionals Data System
  - American Medical Association
  - American Hospital Association
  - National Profile of Local Health Departments*

- **Sources of data on patient-level demographics, risk factors, and tumor information**
  - North Carolina Central Cancer Registry
  - Federal and private payer claims
  - Other registries
  - Linked cancer-related cohorts

**Integrated reference data and crosswalks**
- ICD-9, ICD-10 codes
- CPT/HCPCS codes
- LOINC data
- ZIP codes, ZIP Code Tabulation Areas, Health Service Areas, and US Census data

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*Compiled by the National Association of County and City Health Officials.

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measures and study feasibility. The easy-to-navigate Web interface allows users to save reports, maps, or tables and to share them with other users.

**Secure data analysis platform.** ICISS operates a secure data analysis platform in collaboration with UNC Information Technology Services. This infrastructure enhances accessibility through remote virtual desktops, gets new users up and running quickly, delivers extremely fast data transfer, and centralizes licenses and installations of tools (eg, SAS, R, ArcGIS). Users connect to ICISS through 2-factor authentication. Secure data access is managed centrally at ICISS, and levels of access are individualized for each user based on the user's role, his or her Data Use Agreement, and IRB governance requirements.

**Research tracking system.** The central research tracking system promotes consistent study governance and allows project managers to oversee research operations and activities. It provides electronic capture and review of proposals, letters of intent, IRB applications, and grant proposals. It can also track the progress and deliverables of ongoing projects, including abstracts and publications, and it can assign tasks across a matrix team. The system is customized to triage and streamline requests for data access.

**ICISS Research and Methods**

An interdisciplinary "team science" approach is required for resources such as ICISS to operate efficiently and effectively [14, 16-18]. The ICISS team includes computer scientists, clinicians, biostatisticians, epidemiologists, health services researchers, demographers, and geographers trained at the MD, PhD, and master's degree levels. The team is fully integrated, and individuals work together to share diverse ideas and to develop and optimize novel inter-disciplinary solutions for managing, leveraging, and lifting complex data sets into analytic files for research studies.

**Research scope.** The ICISS data and the ICISS team enable a diverse portfolio of research. ICISS is currently being used for studies of comparative effectiveness (eg, the article by Goyal and colleagues on pages 231–238), treatment disparities [10, 19], access to care [8], and investments within the public health system (eg, a 2011 study by Mays and Smith [20], which linked increases in public health spending to declines in preventable deaths). The availability of longitudinal data allows researchers to examine the effect of health policies such as Medicare Part D or the Patient Protection and Affordable Care Act of 2010, as well as temporal trends such as the 2008 economic recession [21]. Disease incidence, risk of late effects of treatment, and rare diseases can also be studied by applying novel geospatial statistical methods (eg, a 2011 study by Ku and colleagues [22], which reported geographic disparities in late-stage breast cancer diagnosis).

**Population-based and advanced methods.** ICISS is uniquely positioned to support the development of new, advanced analytic methods that will extend the reach of its research potential. For example, ICISS can be used to study the different types of bias that exist in observational studies [23]. Multipayer data allow researchers to examine the selection and confounding biases found in single-payer data (eg, Medicare) or clinical trials, as well as patient heterogeneity and differential patient outcomes [24-27]. ICISS data also enable exploration of instrumental variables for control of unmeasured confounding [28-31], causal modeling [32, 33], systems modeling (ie, agent-based models), or application of social network analysis (ie, care coordination [34]). Finally, ICISS is facilitating work in advanced data mining and data visualization by collaborating with computer scientists, informaticians, and biostatisticians.

**Data integration.** ICISS continues to develop novel methods of enhancing data, including 3-way and 4-way integration of epidemiologic cohort studies and other registries. This allows a more comprehensive characterization of the measures that are important to the study of cancer care and outcomes, and it substantially expands the research beyond what would be possible with any of the data sets alone. For example, the integrated data allow examination of critical individual-level measures of behavioral risk factors, laboratory results, patient-reported outcomes, and genetic markers—none of which are currently available in registry or claims data [35]. This is opening the door to more personalized medicine and patient-centered research, as well as the development of new methods for creating, managing, and using big data.

**Conclusion**

Effectively using big data for population research requires more than just access to terabytes or petabytes of data. Both technical and human resources are required to operationalize integrated research systems and environments for this type of data resource. Developing such resources requires transdisciplinary collaborations of well-trained professionals who are able to develop novel hypotheses, bridge technical and disciplinary gaps, and communicate effectively to achieve cohesive solutions. Agile and secure computing systems are needed to support the data and to meet the specific requirements of data partners and researchers. Although grant funding can offset some of the costs of personnel, a preliminary investment is essential for data acquisition and development of technical infrastructure and systems. With current data systems in place, a governance structure has been implemented to expand access to ICISS to investigators across the state. Developed through the support of the North Carolina General Assembly and the University Cancer Research Fund, ICISS represents a successful integrated research platform that leverages large, linked, multipayer data sets to improve population health. NCMJ

Anne-Marie Meyer, PhD research assistant professor, Department of Epidemiology, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill; faculty director, Integrated Cancer Information and Surveillance System (ICISS), Lineberger Comprehensive
Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Andrew F. Olshan, PhD distinguished professor, Department of Epidemiology, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, department chair, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Laura Green, MBA project manager, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Adrian Meyer, MS director of systems development, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Stephanie B. Wheeler, PhD, MPH assistant professor, Department of Health Policy and Management, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

Ethan Basch, MD, MSc director, Cancer Outcomes Research Program, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

William R. Carpenter, PhD, MHA faculty director, Lineberger Comprehensive Cancer Center, University of North Carolina at Chapel Hill; associate professor, Department of Health Policy and Management, UNC Gillings School of Global Public Health, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

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The Ethics of Clinical Trials for Cancer Therapy

Lynn J. Howie, Jeffrey M. Peppercorn

Cancer clinical trials are intended to evaluate novel interventions and to improve outcomes. Such research depends on the participation of patients seeking the best options for care. The design, conduct, and analysis of trials must therefore be grounded in an ethical framework that respects and protects the interests of clinical trial participants.

Despite advances in treatment, cancer continues to cause substantial morbidity and mortality in the United States, with more than 1.5 million cases of cancer diagnosed each year [1]. It is estimated that 57,000 new cases of cancer will be diagnosed in North Carolina in 2014 [2]. Clinical trials are central to the development of new treatments to improve cancer care and outcomes. However, clinical trials are designed to answer questions about treatments that do not yet have clearly demonstrated benefits. Therapies tested in clinical trials can have unexpected toxicities, and by definition, the risk-to-benefit ratios of these interventions have not yet been determined. In addition, clinical trials can involve tests or procedures that are performed solely for research purposes and are not otherwise necessary for the care of the patient.

Patients often want to enroll in clinical trials in order to obtain cutting-edge therapy or to gain a chance of clinical improvement that is unlikely with conventional therapy. Physicians may discuss a clinical trial with a patient for these same reasons. However, clinical trials are designed to advance knowledge and to improve care for future generations, and thus they are distinct from routine clinical practice, where the sole goal is to care for the patient. For this reason, cancer clinical trials must consider and adhere to core ethical values—including voluntary informed consent, minimization of harm, and equipoise—and they must take into account researchers’ obligations to both participants and science. By doing so, such trials can lead to improvements in clinical care and advancement of new therapeutics for future patients.

Patient Participation

Patients participate in clinical trials for a variety of reasons. The primary reasons include interest in a new treatment that may provide direct benefit, desire to help others, and trust in the physicians and institutions conducting the research [3, 4]. Despite these motivations, fewer than 2% of cancer patients participate in clinical research [5]. Studies have demonstrated that elderly individuals, those with comorbid conditions, ethnic minorities (including African Americans and Latinos), and those with lower socioeconomic status tend to be underrepresented in cancer clinical trials [5-7]. Barriers to enrollment include concern about adverse effects of unstudied therapies, mistrust of research, financial constraints, lack of availability of trials for treatment of a particular condition, or lack of access to trials [8-10]. In addition, although randomized trials typically test the interventions that appear most promising based on preliminary efficacy and safety data, patients may be confused by the concept of randomization, they may not like the fact that their doctor will not be directly determining which intervention they receive, or they may be unwilling to risk being assigned to a control arm.

Amid the general concern about low rates of participation in adult oncology trials, there have been recent calls to reinvigorate and reemphasize the recruitment of ethnic minorities to participate in cancer clinical trials, because the persistently low participation rates among these groups is thought to be associated with ongoing disparities in outcomes [11]. In pediatric oncology, rates of clinical trial participation have historically been very high, and the ability to learn from virtually every patient is credited with being part of the reason for the high cure rates achieved in pediatric cancers over the past several decades [12].

Types of Clinical Trials

Studies evaluating new therapies occur in several phases to determine whether these agents or interventions merit continued evaluation in larger groups of participants (see Table 1). It is important to understand the phases of cancer trials and to consider the distinct ethical issues that can arise at each step of the process of trying to bring a new intervention to the clinic.

Phase I clinical trials are the first test of an intervention in humans; these trials are performed following preclini-
cal work in cancer cells and in animals. The primary goals of phase I trials are to evaluate dosing and to study the safety of novel therapies; the secondary goal is to determine whether there is evidence of anticancer activity that merits further evaluation in subsequent studies. These relatively small studies raise large ethical issues, because the participants are often relatively healthy patients who have few or no other therapeutic alternatives, who face death in a matter of months without treatment, and who participate with the hope of improved survival [13]. However, these studies involve interventions that are the least tested, and the study may not expose patients to the dose of the drug that will be used in later studies. The difference between the participants’ goals and the scientific goals of phase I cancer trials has created concern regarding therapeutic misconception [14], which is defined as the failure of trial participants to understand that the primary purpose of clinical trials is to produce generalizable scientific knowledge [15]. Behind these ethical concerns is the idea that, if patients truly understood the nature and design of a phase I trial, they might choose not to enroll.

Much has been written about the concept and validity of therapeutic misconception, but as Agrawal and Emmanuel pointed out [16], it may be perfectly reasonable for an informed patient to participate in a phase I trial, given the limited alternatives. The researcher’s ethical obligation is to ensure that participants in a phase I oncology trial understand that the study is research and that drugs tested in phase I clinical trials often have limited efficacy and unexpected toxicities; researchers should also make sure patients know what is and what is not known about the intervention. A systematic review of phase I oncology trials from 1991 through 2002 [17] demonstrated that agents evaluated in phase I trials had an objective tumor response rate of 10.6%; this rate ranged from 4.4% among trials of a single agent to 17.8% among trials that include at least 1 anti-cancer agent that was already approved by the US Food and Drug Administration (FDA). Of the participants for whom grade 4 toxicity data were available, 14.3% experienced at least 1 such toxic event. The highest toxicity-related death rate was found in trials involving multiple chemotherapeutic agents (both investigational and FDA-approved) [17]. Thus there is need for a thorough discussion of the risks, benefits, and alternatives to participation in a phase I trial, including palliative care [13].

Once a phase I trial has proven that an intervention is relatively safe (and ideally that it has potential for disease response), then additional phases of clinical trials are conducted; these are designed to better define safety and effectiveness in larger populations. Phase II clinical trials are typically single-arm studies that test interventions at a dose defined as tolerable by the phase I trial; the goal of phase II trials is to further evaluate safety and to determine whether an agent is effective at controlling disease or symptoms for a specific cancer.

If an intervention still appears safe and effective in phase II trials, then a larger, randomized phase III trial will be conducted to evaluate the novel intervention in comparison with an existing standard of care. In oncology, phase III trials typically test a proven therapy, such as cytotoxic chemotherapy, with or without the addition of a novel therapy.
molecularly targeted intervention). A placebo can be used in a phase III trial when patients in the control arm and those in the experimental arm both receive standard chemotherapy, or a placebo alone can be given to patients in the control arm when there is no clear standard of care or when the existing standard of care is known to have little efficacy and/or has excessive toxicity [18].

Although participation in a clinical trial at any phase may benefit the subject, such studies are designed to determine the best treatment for future patients. Given the uncertainty associated with any experimental intervention, there are potential benefits but also risks associated with participation in clinical trials, including toxicity, lack of efficacy, adverse events from study procedures, financial costs, time burdens, and privacy concerns. As a result, how patients are informed about potential risks and benefits is a central component of the ethical conduct of these trials.

Informed Consent

Informed consent is a necessary, but not sufficient, component of ethical research conduct. For participation in clinical research to be voluntary, patients must understand several aspects of the study: its purpose, the visits and procedures that will take place as a part of the study, the risks and benefits of the study and of the potential interventions, their right to withdraw from study participation at any time, and the alternative treatments that are available if they choose not to participate in the study [19]. Important elements of informed consent are described in the US Code of Federal Regulations [20]. Recent efforts have sought to improve the quality of informed consent through the use of plain language and by having prospective research participants watch videos that enhance their understanding of the study and of the consent process [21, 22].

Scientific Considerations

In addition to considerations pertaining to respect for research subjects as individuals, the scientific aspects of clinical trials also play a role in determining whether a clinical research study is ethical. Study design, study conduct, scientific validity, contribution to scientific knowledge, and communication and dissemination of results are all parts of ethical research conduct [23]. Ethical research studies must be scientifically rigorous and designed in such a way that they will be able to answer the questions they pose; fulfilling these criteria helps to justify patients’ participation in the study and the risks that they accept in exchange for contributing to scientific knowledge.

Study design. For a clinical trial to be ethical, it must possess the quality of clinical equipoise, meaning that there is no existing evidence suggesting that participation in one treatment arm will result in inferior results compared with participation in another treatment arm [24]. This equipoise should be present throughout the trial; if it becomes evident that one of the treatment arms is inferior to the other, then the design of the trial should be modified to eliminate the inferior treatment. This modification, which can be done through adaptive clinical trial designs or interim analyses, should ensure that subjects enrolled in a study are not exposed to treatments that have been demonstrated to be worse than alternatives within the trial design.

As data are collected and evaluated for interim safety and efficacy analyses, researchers may face decisions about discontinuing a trial early due to evidence of harm, evidence of futility, or evidence of superior efficacy. The ethical need to not harm current research subjects, whether by exposing them to risky medications or by preventing them from receiving therapies that appear to be clearly superior, can conflict with the need to better understand the risks and benefits of the treatment over time [25]. However, given that participants have the right to withdraw, there should be established ways of notifying them of new information obtained during the trial, particularly information about potential treatment risks, so that informed consent is present throughout the subject’s participation [26].

Scientific obligations. When a clinical trial is completed, researchers have a duty to report the results so that the study can inform oncologists and patients about the suitability of the experimental intervention as a possible addition to standard cancer care. Unfortunately, a significant number of trials are not reported in journal publications, which results in biased reporting of available data [27]. Additionally, preliminary data that are reported at scientific meetings are often not followed by journal publications, suggesting that analysis of additional data changed the magnitude and/or direction of the impact of the therapy [28]. This lack of published studies has substantial implications for the way that new therapeutics are incorporated into routine clinical practice and how information about safety or efficacy is understood.

Ethical Issues With Emerging Research Practices

While our focus has been on the ethical issues associated with traditional cancer clinical trials, we should also acknowledge the increased interest in using “real world” data from electronic health records (EHRs) and administrative data to better understand the effectiveness and safety of cancer interventions in clinical practice. This is of particular interest in oncology, where patients enrolled in trials are often younger and healthier than the average cancer patient, and because there is considerable off-label treatment in settings where a large randomized trial may never be done [29]. Given that EHRs are used in routine clinical practice, issues concerning consent to data usage and patient privacy are of central concern when data are used for research. The ethical frameworks to address these concerns are developing, with a central focus on the balance between protecting patient privacy and the potential public good that might result from this research, such as safety data and comparative effectiveness evidence, which could lead to improved outcomes and reduced societal costs of care [30].
Conclusions

Clinical trials are essential to improving outcomes for future generations of patients with cancer. Such trials also offer participating patients access to a treatment within a carefully regulated environment with an emphasis on safety. A clinical trial participant may be among the first to benefit from a novel intervention that is not otherwise available. However, given the uncertain nature of the outcomes for individual participants in these trials, adherence to ethical principles in study design and conduct is needed to ensure that participants are being treated with autonomy and respect, and that the study is contributing to knowledge that will help guide care for future patients.

Advances in cancer care over the past 50 years have come primarily through clinical trials. Further research, conducted on a solid ethical foundation, is essential to continue this progress. Patients with cancer should be offered the opportunity to consider participation in clinical trials whenever possible, and they should be provided with the information they need to make an informed choice about whether enrollment in such a trial is right for them.

References

INVITED COMMENTARY

Expanding Use of Palliative Care in the Oncology Setting

Janet H. Bull, Amy P. Abernethy

The use of palliative care for patients with serious disease improves quality of life, reduces symptoms, and saves money. Unfortunately, too many patients endure needless suffering. Expanding awareness about palliative care among patients, providers, and policymakers will hopefully generate momentum for use of such services, thus benefitting patients with cancer and other advanced diseases.

From the first day of medical school, physicians are taught that they should focus on curing a patient’s underlying disease. Relieving symptoms and improving overall quality of life are often viewed as byproducts of eradicating illness—goals to be hoped for, but a secondary focus at best. In reality, both diseases and their accompanying treatments can lead to increased symptom burden and associated suffering. This is particularly true in cases of advanced serious illness, which not only threatens longevity but also is punctuated by challenging symptoms, progressive loss of function, existential concerns, and multiple threats to quality of life.

When symptoms, medication side effects, and functional status worsen, a palliative care specialist may be called in to help with the patient’s care. The palliative care team takes a holistic approach—addressing the physical, psychological, social, and spiritual domains of care—with a focus on enhancing quality of life. Unfortunately, about 70% of Americans have little understanding of palliative care, and many physicians still incorrectly equate palliative care with hospice care. This leads to late referrals at the end of life, after curative life-prolonging care has failed [1].

The term palliative comes from the Latin word palliare, meaning “to cloak.” Palliative care, which may also be referred to as supportive care, focuses on relief of pain and symptoms, discussion of goals of care, advance care planning, emotional and spiritual care, caregiver support, and navigation of a fragmented health care system. Palliative care may be provided along with curative care, or palliative care may be the sole focus, depending on the needs of the individual. As illness progresses and death nears, the proportion of the sick person’s health care that is palliative in focus increases, until palliative care becomes the dominant type of health care in the later stages of illness (see Figure 1).

There is much confusion about the difference between palliative care and hospice care. As Figure 1 shows, hospice care and bereavement are parts of palliative care. The easiest way to think about this continuum is to realize that hospice care is a kind of palliative care that is typically provided when the ill person is in the last weeks to months of life. Practically speaking, the differentiating features are a byproduct of reimbursement mechanisms—specifically, how Medicare pays for end-of-life care. To qualify for hospice care under the Medicare hospice benefit, the patient must have no more than 6 months to live (a prognosis that must be confirmed by 2 physicians), and the focus of treatment must be noncurative care and comfort. Although hospice care is appropriate for patients in the last 6 months of life, hospice care is underutilized, with approximately one-third of patients dying within 1 week of first receiving palliative care services. In 2012, the average length of stay for patients in hospice care was 71.8 days, with a median length of stay of 18.7 days [2]. By diagnosis, cancer patients have shorter lengths of stay (53 days) than patients with neurological conditions (132 days), chronic obstructive pulmonary disease (107 days), debility (98 days), or heart/circulation diagnoses (76 days) [3]. Hospice care at the end of life is considered to be the gold standard for high-quality care, and it has been demonstrated that palliative care increases access to hospice services [4].

In contrast to hospice care, palliative care is reimbursed by the same mechanisms used to reimburse curative care (eg, fee-for-service reimbursement, reimbursement as a hospital-funded consultation service, or reimbursement as part of a bundled payment benefit). Unfortunately, the misperception that palliative care is the same as end-of-life care means that patients with serious illnesses who have longer prognoses and are continuing to receive curative treatments may miss out on the chance to receive palliative care. Ideally, palliative care should begin early in the disease process, preferably when a patient is first diagnosed with a chronic, debilitating, or life-threatening illness.

Palliative care takes a patient-centered approach and...
focuses on treating a patient with dignity and respect while understanding his or her values and cultural beliefs. In the traditional medical system, providers often talk about lung cancer patients as if they were all the same, since the physician's focus is on the illness. In a patient-centered approach, the focus is on the particular patient with lung cancer: What are his or her beliefs, treatment goals, preferences, hopes, and fears? How does the patient fit within his or her family structure? Understanding these key concepts helps providers deliver individualized care that is consistent with what is important to the patient.

Palliative care is best delivered by a team of specialized individuals. Core members of this team should include physicians, nurse practitioners, physician assistants, nurses, social workers, chaplains, and the patient and family. Psychologists, physical and occupational therapists, dieticians, and pharmacists may also be included as part of the expanded team. Interdisciplinary care involves incorporating the patient and family in decision making, determining values that direct the goals of the care plan, collaborating and using the expertise of various disciplines, and identifying appropriate interventions that align with the holistic nature of care. Palliative care can be offered in any care setting and is best when delivered across the continuum of care. Many cancer centers now embed palliative care teams in their clinic settings.

When the palliative care team is involved early, the benefits to patients and families are widespread and impressive. Studies of palliative care have found a significant reduction in symptom distress [5-7], lower rates of emergency department visits [8, 9], fewer and shorter hospital and intensive care unit admissions [8, 10], better mood and less depression [11, 12], enhanced quality of life [5, 11, 12], and a longer median duration of survival [12]. Conducting end-of-life discussions with patients has been associated with significant reductions in use of ventilation, resuscitation, and intensive care, and having such conversations increases the likelihood that patients will be enrolled in outpatient hospice for longer than 1 week [13]. Other studies confirm that palliative care helps clarify the patient’s assessment of his or her diagnosis, which contributes to less aggressive end-of-life care and less resource utilization [12, 14].

Accordingly, a byproduct of palliative care is a reduction in the cost of care [8, 10, 15]. Although cost saving is never the reason for consulting palliative care specialists, initiating palliative care early—rather than after all else has failed—can reduce health care expenses. Specifically, use of palliative care has been shown to reduce spending on inpatient care (by as much as $2,500 per admission [16]), to reduce spending on outpatient care (by 33% per patient [8]), and to result in less use of acute care services, fewer admissions, fewer emergency department visits [12, 17], and overall cost reductions at the end of life [18, 19]. Finally, palliative care is associated with greater satisfaction on the part of patients and families [5]. Table 1 lists typical quality measures for palliative care.

Given these favorable outcomes, it is somewhat surprising that utilization of palliative care is not higher. In 2011, hospital-based palliative care was available in 63% of US hospitals with more than 50 beds—an increase of 138% since 2000 [20]. In North Carolina, 94% of hospitals with at least 300 beds offer palliative care, and 75% of hospitals with at least 50 beds have a palliative care service [21]. However, smaller, public, or for-profit hospitals are significantly less likely to offer palliative care [22]. Another challenge is that many of the people who need palliative care are not in the hospital, and outpatient palliative care is not yet widely practiced, despite the benefits realized by patients who are able to remain at home [12, 23-26]. For example, in 2011 only 8% of hospitals in California supported an outpatient palliative care program [27].

One of the main reasons why adoption of palliative care (outside of hospice) has been slow is that reimbursement models continue to be unclear and erratic. Four Seasons, a nonprofit organization in Western North Carolina that delivers palliative care to a large population, has outlined a sustainability model for community palliative care [28]. Such models need to be tested to determine their practicality, effect on

TABLE 1. Measures of the Quality of Palliative Care

<table>
<thead>
<tr>
<th>Types of measures</th>
<th>Examples</th>
</tr>
</thead>
<tbody>
<tr>
<td>Symptoms</td>
<td>Pain, fatigue, dyspnea, nausea, depression, anxiety, insomnia, dysphagia, constipation</td>
</tr>
<tr>
<td>Advance care planning</td>
<td>DNR form signed, health care surrogate designated, MOST form signed</td>
</tr>
<tr>
<td>Psychosocial and spiritual factors</td>
<td>Emotional well-being, quality of life, spiritual well-being</td>
</tr>
<tr>
<td>Functional status</td>
<td>Palliative Performance Scale*</td>
</tr>
</tbody>
</table>

Note. DNR, do not resuscitate; MOST, medical orders for scope of treatment.

*The Palliative Performance Scale (PPS) uses 5 observer-rated domains (ambulation, activity level, self care, intake, and level of consciousness) and is correlated to the Karnofsky tool. The PPS has been validated and correlates well with actual survival times with cancer patients. More information about the PPS is available on the Medical College of Wisconsin Web site (http://www.eperc.mcw.edu/EPERC/FastFactsIndex/ff_125.htm).
Pediatric Oncology and Palliative Care

Ray Barfield

Overall, we now cure 70% of the children who are diagnosed with cancer, and in the 30% of cases that are still not curable, we can almost always add time to the child’s life. As our ability to cure cancer has improved, we are now paying increased attention to the goal of avoiding or alleviating the suffering associated with cancer and its therapy. Risk stratification aims to avoid undertreatment of children with high-risk cancers and to avoid overtreatment (with all of the associated side effects of therapy) of children with lower-risk cancers. This goal has become an important part of designing treatment protocols over the past 15 years.

Whether or not a child will be cured, we know that all children with cancer suffer, as do their families. Pediatric oncology is committed to curing cancer, but palliative care is committed to improving a child’s quality of life, irrespective of the potential for cure. Oncology and palliative care are thus twin endeavors, both of which seek what is best for a child and his or her family [1]. Within the 2 broad categories of curing disease and alleviating suffering, there are many specific goals unique to each patient. Palliative care seeks to relieve the physical, emotional, social, and spiritual distress produced by complex, chronic, or life-limiting conditions; to assist in making difficult decisions and setting goals; and to enhance children’s quality of life [2].

More than a decade has passed since the American Academy of Pediatrics [3] and the Institute of Medicine of the National Academies [4] called for the integration of palliative care into ongoing medical management of life-threatening illnesses (such as cancer) in children, from diagnosis to the end of life. Since these calls were issued, models of integrated pediatric palliative care have been developed in which curative therapy and palliative care coexist. For children whose lives are going to be short, adding a few months of good-quality life can be transformative. Adding 6 months to the life of a child who would otherwise have died at 3.5 years of age is extending his or her life by nearly 15%.

To help maximize both quantity and quality of life for children with terminal illnesses, the Patient Protection and Affordable Care Act of 2010 contains the Concurrent Care for Children Requirement [5]. This provision states that palliative and hospice care services must be reimbursed if they are administered to a child with a life-limiting illness who is eligible for Medicaid or the Children’s Health Insurance Program, even if the child is still receiving disease-modifying treatments. In this context, concurrent care is defined as the introduction of palliative care principles at the time of a life-threatening diagnosis, with increasing support over time as the disease progresses; this approach includes a multidimensional assessment to identify, prevent, and alleviate suffering [6]. At the end of life, the model allows for hospice services without requiring the patient to stop all traditional medicine, which may include antibiotics, transfusions, and palliative chemotherapy.

Such models have been supported by studies of adult patients that have demonstrated that palliative care prolongs life [7], is effective in improving quality of life and mood [8], and decreases caregiver burden [9, 10]. In 2012 the American Society of Clinical Oncology released a provisional clinical opinion, based on available evidence from clinical trials, advocating for the early integration of palliative care into standard cancer treatment for malignancies with high symptom burden [11]. However, many challenges exist in the implementation of these integrated models, patients and families, and financial impact on the health system. Although North Carolina’s Medicaid program and most plans offered by Blue Cross and Blue Shield of North Carolina cover palliative care consultations on a fee-for-service basis, the amount of money reimbursed does not cover the cost of running a palliative care program, which is why there are currently few community programs that offer such services.

The lack of widespread adoption of palliative care suggests that barriers to implementation are impeding uptake. The most notable barrier is the difficulty of introducing the topic. Many physicians are uncomfortable conducting end-of-life conversations with their patients [29], and they receive little medical training in communication skills such as breaking bad news or delivering prognoses. In a large study of physicians caring for hospice patients with cancer [30], the predicted survival estimates communicated to patients were 3.5 times greater than actual life expectancy, and the closer the physician-patient relationship, the greater the overestimate. Without accurate information, patients often die in places they would not choose while receiving treatments that offer little benefit.

Another roadblock is the hesitancy of policymakers to address end-of-life care. Public misperceptions and finger-pointing about “death panels” during debates over the Patient Protection and Affordable Care Act of 2010 spooked advocates and resulted in legislators subsequently becoming more guarded. Change is in the air, however; there is early bipartisan support for the Patient Centered Quality Care for Life Act [31] and for the Palliative Care and Hospice Education and Training Act [32], both of which currently rest with the Health Subcommittee of the House Energy and Commerce committee. Passage of the latter bill would increase funding for training of the palliative care clinical workforce and would bring attention to important palliative care needs of patients and families.

One further roadblock can be best summarized as lack
including the pressure to reduce overall health care costs, lack of necessary tools and skills on the part of health care providers, and the mistaken tendency to equate palliative care with end-of-life care.

The Concurrent Care for Children Requirement has been challenging to implement in many states, including North Carolina. Despite the fact that palliative care is now widely recognized as a critical part of excellent care for children with life-limiting diseases such as cancer, patients continue to receive this care very late in their illness trajectory [12, 13]. In 1 study, the median time between palliative care consultation and death was only 8 days [14]. However, as evidence grows that introducing palliative care early in the course of therapy benefits children with cancer, and as the medical culture becomes more aware of the evidence demonstrating the value of such an approach, pediatric oncology and palliative care will continue to become more integrated. This will benefit children, their families, and the staff members who care for them. NCMJ

Ray Barfield, MD, PhD associate professor; Department of Pediatrics, Duke University, Durham, North Carolina.

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Address correspondence to Dr. Ray Barfield, Duke University, 2 Chapel Dr, 0024 Westbrook Bldg, Durham, NC 27708 (rbarfield@div.duke.edu).

N C Med J. 2014;75(4):276-277. ©2014 by the North Carolina Institute of Medicine and The Duke Endowment. All rights reserved. 0029-2559/2014/75411 of awareness. Without public and clinical understanding of the role of palliative care, it is hard to expand its availability. Therefore, multiple clinical professional organizations have sought to increase awareness of palliative care among their members.

For example, in 2012 the American Society for Clinical Oncology issued a provisional clinical opinion about integrating palliative care into the standard practice of oncology [33]. This document makes the following points: First, palliative care leads to better patient and caregiver outcomes, including symptom improvement, better quality of life, greater patient satisfaction, and reduced caregiver burden. These benefits can be achieved either when palliative care is used in combination with standard cancer care or when palliative care is the main focus of care. Second, when palliative care is provided early in the treatment trajectory, referrals to and use of hospice care are more appropriate, and futile use of intensive care is reduced. Third, no trials to date have demonstrated harm to patients and caregivers, or excessive costs, from early involvement of palliative care. Fourth, patients with metastatic non–small-cell lung cancer should be offered standard oncologic care and concurrent palliative care, preferably at the time of the initial diagnosis. Fifth, standard oncologic care and palliative care should be combined early in the course of illness for patients with metastatic cancer and/or high symptom burden. Finally, future research should focus on how early palliative care impacts essential patient and caregiver outcomes (eg, quality of life, survival, utilization of health care services, and costs) and how it impacts society.

The potential benefits of palliative care to patients and families often remain unrealized and underappreciated. The limited penetration of palliative care into mainstream treatment of serious disease—despite the evidence that palliative care results in better quality of life, reduction of symptom load, and cost savings—means that an inordinately high fraction of patients with serious illness will endure needless suffering. Hopefully the expanding base of compelling evi-
dence regarding palliative care will raise awareness of the benefits of such care among patients, providers, and policymakers. NCMJ

Janet H. Bull, MD chief medical officer, Four Seasons Compassion For Life, Flat Rock, North Carolina. Amy P. Abernethy, MD, PhD director, Center for Learning Health Care, Duke Clinical Research Institute, Durham, North Carolina.

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INVITED COMMENTARY

Living With Advanced Cancer: Unmet Survivorship Needs

Eliza M. Park, Donald L. Rosenstein

Most cancer survivorship initiatives are designed for patients whose treatment is intended to be curative. For patients living with advanced cancer, in contrast, survivorship research efforts and programs are far less common. This neglected aspect of cancer survivorship requires particular emphasis on active symptom management and clarification of goals of care.

The month of October, with its emphasis on early detection and celebration of lives saved—with cheery pink everything—felt happy to me. All of this changed in May 2010. All of a sudden I was no longer a happy success story of early detection. The happy pink month of October became a sort of taunt rather than a celebratory time, and I had no idea where I fit in when people were lining up by years of survivorship. Am I a survivor still? Fortunately, thanks to the best medical care available and a whole-system approach to healing, I am still alive today, almost 4 years later, but incurable cancer with never-ending treatment affects my entire life. My partner and teenage children live with my cancer every day as much as I do and experience its profound effects on their lives. The ups and downs of struggles with receiving news about the cancer and its progression, my variability in being able to be fully present with my family, and the ongoing uncertainty about my prognosis affect the entire family.

— PJ, a 54-year-old woman with metastatic breast cancer

Defining Advanced Cancer

Part of the difficulty in identifying the unique survivorship needs of patients with advanced cancer is the challenge of defining this heterogeneous population. For this commentary, we consider advanced cancer survivors to be individuals living with either an incurable cancer (ie, a solid tumor with distant metastases) or chronic cancer (eg, chronic lymphocytic leukemia). Different cancer advocacy and funding organizations, as well as individuals affected by cancer, define cancer survivors in various ways. The National Coalition for Cancer Survivorship defines survivorship as beginning at the time of diagnosis and continuing through the balance of the person’s life; because family members, friends, and caregivers are impacted by the survivorship experience, they are also included in this definition [4]. Such a broad conceptualization encompasses men and women who are cancer-free as well as those living with cancer, either continuously or intermittently. Unsurprisingly, many patients have not embraced the term cancer survivor —either because it is too early in their journey to know whether they will survive or because it has become painfully clear that they will not. In an international survey of 1,342 women with metastatic breast cancer, the results of which were published in 2010 [5], 61% of respondents considered themselves to be cancer survivors.

The unique needs of patients with life-limiting or chronic cancer are rarely emphasized in current approaches to cancer survivorship, yet the number of such patients is growing, as improvements in cancer treatment allow patients with advanced cancer to live longer. For example, the 5-year survival rate for metastatic breast cancer was 10% in the 1970s. Today, as many as 23% of patients with metastatic breast cancer will survive for at least 5 years [6], and it is estimated that more than 150,000 women and men are living with metastatic breast cancer in the United States [7]. Similarly, targeted therapies for diseases such as chronic myeloid leukemia [8] and metastatic colorectal cancer [9] have led to significant improvements in survival. We con-
tend that growing numbers of cancer patients fall into a gap between survivorship programs, which are focused on wellness and surveillance, and end-of-life specialty care.

Emerging survivorship research and programmatic priorities, such as treatment summaries and care plans, may hold less relevance for patients living with advanced cancer. For example, a major component of survivorship recommendations is the combination of screening for new malignancies and surveillance for recurrence [10, 11], but this is of no consequence for patients with widely metastatic disease. Once the prospect of cure is no longer realistic, clinical priorities appropriately shift to clarifying goals of care, extending life, managing physical symptoms, fostering psychological adaptation, and maximizing quality of life. The challenges of spiritual distress and medical decision making also come to the forefront in this group, as disease progression forces these individuals to face new dilemmas.

Symptom Burden

Available data reveal that patients living with advanced cancer experience a substantial burden of physical and psychological symptoms that can profoundly affect their quality of life. In a systematic review published in 2007 [12], symptom prevalence was assessed in more than 25,000 patients with incurable cancer, and these patients commonly cited symptoms of fatigue (74%), pain (71%), lack of energy (69%), weakness (60%), and appetite loss (53%). Similarly, a 2007 meta-analysis published in *Annals of Oncology* [13] estimated that 64% of patients living with advanced, metastatic, or terminal disease experience moderate to severe pain, compared with 33% of cancer patients who had completed curative treatment. These data demonstrate that many patients living with advanced disease experience undertreated somatic symptoms. Patients and their families may not realize that much of this suffering is preventable. Resources such as booklets from the National Cancer Institute—including *Coping with Advanced Cancer* [14] and *When Someone You Love Has Advanced Cancer* [15]—are helpful recent contributions. Still, we are long overdue for improved advocacy efforts and detailed guidelines on symptom management in advanced cancer.

Another shortcoming is that traditional methods of assessing symptom burden and functional status may underestimate the degree of disability experienced by patients with metastatic disease. In a recent study of cardiopulmonary function in breast cancer survivors, Jones and colleagues [16] found that quantitative cardiopulmonary exercise testing revealed marked functional impairment as measured by peak oxygen consumption, although these survivors had normal cardiac function as measured by left ventricular ejection fraction. The impairment was significantly greater in the cohort of survivors with metastatic disease than in the cohort of women with nonmetastatic disease [16]. Furthermore, untreated symptoms rarely occur in isolation; most patients who experience significant physical symptom burden also face challenges due to the lifestyle and psychosocial changes that accompany their illness.

The psychological adaptation to living with incurable disease can present challenges that are as great or greater than the physical consequences of advanced cancer and its treatment. Within the context of cancer survivorship, patients with advanced disease often feel marginalized or isolated [17, 18]. Approximately 20% of all patients with advanced cancer have symptoms consistent with a depressive disorder, and nearly 14% meet diagnostic criteria for an anxiety disorder [19]. Sources of emotional distress in this group typically differ from those of patients with earlier-stage disease. Psychological concerns—such as distress over anticipated death, fear of being a burden to loved ones, and social isolation—take on heightened meaning for these patients.

Coordination of Care

Given the magnitude and persistent nature of treatment and symptom burden in patients with advanced cancer, a coordinated team approach is needed to achieve compassionate and cost-effective treatment. Coordination of care (e.g., between the patient’s oncologist and his or her primary care provider) is one of the most important and problematic aspects of cancer survivorship [11]. Several studies have suggested that survivors often fail to receive recommended post-treatment care [20-22]. Improved coordination of care holds the promise of decreasing survivors’ exposure to medically unnecessary or duplicate testing [23]. The possibility of participating in a clinical trial is another unique aspect of care coordination for patients with advanced cancer (and those for whom standard care approaches have failed). Here the challenge is to balance current treatment options and outcomes with optimal timing of and eligibility for investigational treatment opportunities. VT, a patient with advanced ovarian cancer, illustrates this challenge when she says, “I realize now that what I should have done was look for a clinical trial before my last course of gemcitabine. It turns out that I’ve had too many courses of chemo and developed too much toxicity to qualify for the clinical trial I really wanted.”

Emerging models of palliative care can inform how we approach advanced cancer survivorship. Many patients with advanced cancer live for months or years with excellent performance status. For these patients, a survivorship orientation based on the notion that patients will live for decades is no more appropriate than a recommendation to “get one’s affairs in order” and pursue “comfort care.” Patients with advanced cancer deserve full membership in the global survivorship movement.

Survivorship programs must embrace modern palliative care and incorporate its central tenets: aggressive symptom management, clarification of goals of care, and improved communication between and among patients, caregivers, and providers. In 2010 a randomized controlled trial of early palliative care for patients with metastatic non–small-cell lung cancer [24] demonstrated clinically meaningful

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Coping with Advanced Cancer

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Survivorship programs must embrace modern palliative care and incorporate its central tenets: aggressive symptom management, clarification of goals of care, and improved communication between and among patients, caregivers, and providers. In 2010 a randomized controlled trial of early palliative care for patients with metastatic non–small-cell lung cancer [24] demonstrated clinically meaningful
improvements in quality of life, mood, and survival compared with patients who received standard care. Other studies [25, 26] have also demonstrated that early introduction of palliative care improves quality of life. As a result, the American Society of Clinical Oncology recommended in 2012 that palliative care be integrated into standard oncologic care from the time a person is diagnosed with metastatic or advanced cancer [27].

Integrated palliative care has been shown to yield substantial improvements in patient outcomes, but we do not yet know how to best tailor palliative and supportive care for patient subgroups or how to identify strategies to enhance patients' trust and willingness to engage in this treatment. A single approach to palliative medicine will not address all patient needs. As cancer care has become targeted, so too can supportive care. There is also a lack of customized palliative care for specific populations, such as parents with dependent children, adolescents and young adults, and older adults.

Future Directions

A dedicated effort is needed to raise awareness of the psychosocial consequences of living with advanced cancer and to identify strategies to improve quality of life and medical care for this unique group. Policies, research initiatives, and programs that deliver optimal care to these individuals are overdue. Validated clinical interventions for cancer survivors who have completed curative therapy may also hold promise for patients living with advanced disease. For example, a promising area of future research is the value of physical exercise in promoting longevity and quality of life among advanced cancer patients [28, 29]. Further evaluation of psychosocial support interventions also merits attention. Although early research [30] indicated that participation in supportive-expressive group therapy might prolong survival for women with metastatic breast cancer, more recent evidence [31-33] suggests that it does not influence survival but does improve mood and pain perception—particularly among those who have higher distress at baseline. Finally, we wholeheartedly endorse the growing national movement of patient- and family-centered cancer care, which has increasingly recruited patients and caregivers into the operations of cancer centers. The voices of cancer-free patients are invaluable to clinicians and administrators in designing better ways to provide oncology care, as are the insightful perspectives offered by those with incurable cancer.

To sum up, patients with life-limiting or chronic cancer constitute a unique and neglected group of survivors whose needs have been largely unmet. However, we can help these patients live their lives as comfortably and meaningfully as possible through new models of survivorship care and the adoption of modern palliative care principles. Survivorship programs for patients living with advanced cancer should attend to the specific needs of young adult populations and should more actively address the psychological impact of cancer on patients and their families. Clinical program and research strategies to preserve performance status and minimize somatic symptoms are needed for these neglected patients. NCMJ

Eliza M. Park, MD assistant professor, Department of Psychiatry, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina. Donald L. Rosenstein, MD director, Comprehensive Cancer Support Program, University of North Carolina at Chapel Hill; professor, Departments of Psychiatry and Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina.

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References


The physical and mental health of cancer patients needs to be addressed not only during active treatment but also throughout the continuum of survivorship care. This commentary provides an overview of issues pertinent to cancer survivors, with an emphasis on mental health issues and recommendations for annual clinical screening and monitoring using recently published guidelines from the American Society of Clinical Oncology.

Cancer is a major health concern in North Carolina. In 2014 there will be an estimated 57,000 new cancer diagnoses and approximately 20,000 cancer deaths in the state [1]. Due to increases in early detection and advances in cancer treatments, an increasing number of cancer patients will be long-term survivors. Currently, there are approximately 13.7 million cancer survivors in the United States, and this number is estimated to increase to 18 million by 2022 [2]. North Carolina is no exception to this trend, and the total number of cancer survivors in the state was estimated to be approximately 330,000 in 2012 [3]. The majority of long-term cancer survivors are those with breast, prostate, colorectal, or gynecologic cancers [3]. The growing number of cancer survivors will pose challenges for health care systems seeking to meet these patients’ long-term health care needs.

Cancer survivors face unique short-term and long-term challenges to physical and mental health, family functioning, and maintenance of a healthy lifestyle [4, 5]. Long-term and late effects of cancer treatment may arise during or after treatment and may persist throughout a patient’s lifetime. Survivors may also need ongoing monitoring for cancer recurrence and the development of new cancers. Thus cancer can be perceived as a chronic condition, and recommendations are emerging for long-term survivorship care. Cancer survivors who have other chronic conditions or health risk factors at the time of diagnosis may face additional challenges during cancer treatment and follow-up care.

Most research on the quality of life of cancer survivors has been completed in the past decade, with the majority of studies focusing on women with breast cancer [6]. The purpose of this commentary is to provide an overview of factors that affect health-related quality of life in cancer survivors, with a particular focus on mental health issues.

Factors Affecting Quality of Life in Cancer Survivors

**Symptoms and physical functioning.** Studies of quality of life in cancer survivors have examined both the physical and mental health consequences of cancer and its treatments. In general, health care providers have focused largely on patients’ physical symptoms and physical health status, and less emphasis has been placed on mental health issues [7]. Physical symptoms vary across cancer types and treatment modalities but commonly include fatigue, sleep disturbances, pain, nausea and/or vomiting, diarrhea, neuropathy, skin rashes or toxicity, cachexia, arthralgias, myalgias, lymphedema, impaired sexual functioning, and cognitive problems [5, 6]. How these symptoms impact quality of life varies depending on a number of factors, including the type and stage of cancer at diagnosis, the patient’s prognosis, the type of treatments received, the patient’s age, and comorbidities (both before and after the cancer diagnosis). Socioeconomic status and access to care also affect receipt of effective treatment and relief of symptoms. Recent longitudinal research shows that many physical symptoms persist long beyond the initial treatment period and may influence survivors’ quality of life throughout the remainder of their lives. In addition, conditions such as cardiotoxicity and accompanying symptoms can develop 10 years or more after treatment, indicating the need for long-term surveillance of and specialized care for cancer survivors. Even long after diagnosis, cancer survivors are significantly more likely than adults without cancer to be in poor health and to have multiple chronic medical conditions and functional and employment limitations [8, 9].

**Mental health and well-being.** For cancer survivors, as for individuals without a history of cancer, physical health directly influences mental health status and overall quality of life. Physical symptoms are more likely to be detected and treated by health care providers, as the mental health...
and social consequences of illness are less well recognized. However, poor mental health is the leading cause of disability in the United States; nearly half of US adults will develop mental illness at some point in their lives, and the economic cost of mental illness in the United States was approximately $300 billion in 2002 [10]. Poor mental health is even more prevalent among those with chronic illnesses [11]. In responses to the 2010 National Health Interview Survey, 10.1% of cancer survivors reported poor mental-health–related quality of life, compared with only 5.9% of adults without cancer [12]. Population-based data suggest that cancer survivors are more than twice as likely to have disabling psychological problems compared with adults without cancer, and individuals who have both cancer and other chronic illnesses have a risk of psychological disability that is nearly 6 times higher than that of adults without cancer [8].

Risk factors for poorer mental-health–related quality of life among cancer survivors include younger age, less education, a greater number of noncancer medical conditions, lower income, and not being partnered or married [12-15]. Whether there are racial or ethnic differences in mental-health–related quality of life among cancer survivors remains unclear. Several studies have found no racial/ethnic differences [12, 13]; other studies have found that African Americans (commonly breast cancer survivors) report better emotional well-being than whites [16]; and a few studies have reported lower mental-health–related quality of life among Hispanics, Asian Americans, or African Americans [13, 14]. Poor mental health is associated with risk factors and poor outcomes in the general population, where associations have been found between depression and nonadherence to medical treatment [17] and between depression and increased use of medical services [18]; similar associations have been found among cancer survivors, in whom depression has been found to be associated with maladaptive health behaviors and poorer overall survival [19].

Cancer diagnosis and treatment may be accompanied by profound physical, emotional, social, occupational, and financial stressors, as well as associated increases in anxiety and depressive symptoms. The first 1–3 years after treatment are a critical period during which to monitor the mental health of cancer survivors. Challenges during the early post-treatment period may include a shift in the focus of medical care (eg, from “fighting cancer” to surveillance, recovery, or wellness), fear of recurrence, resumption or alteration of life roles, late and long-term effects of treatment (which can be physical and/or psychological), perceived loss of support from providers, and diminished instrumental and emotional support from family and friends [20]. Long-term survivors may face psychological challenges associated with cancer recurrence or second cancers, as well as continuation of mental health symptoms that first occurred during diagnosis and treatment.

Most of the longitudinal research on mental health trajectories among cancer survivors has focused on the first year after diagnosis with breast cancer [21], although several studies have examined trajectories of mental health after treatment (from 8 to 55 months after diagnosis) [22, 23]. Studies have generally found trajectories indicating persistently good or poor mental health over time, but there are also some groups of women who experience significant declines or improvements in mental health in the years following diagnosis. Factors associated with better adjustment have included older age, being married or partnered, greater optimism, greater self-efficacy, better social support, less rigorous chemotherapy, less pain, and less intrusion of illness on daily life [21-23].

**Age at diagnosis.** Young and middle-aged adults who are diagnosed with cancer face additional stressors and challenges compared with those who receive cancer diagnoses at older ages [24, 25]. Across cancer types, younger age is a risk factor for poorer mental health outcomes. Although never welcome, a cancer diagnosis before age 50 years is less common and is more unexpected for many individuals. Younger women with breast cancer have been studied more than other populations of younger survivors, and we know more about the quality of life of these patients over time than we do about other cancer patients diagnosed as younger adults [26-28]. Among premenopausal breast cancer survivors, quality of life can be disrupted by chemotherapy-induced ovarian dysfunction—which can result in vasomotor symptoms, vaginal dryness, impaired sexual functioning, and sleep problems—as well as symptoms associated with treatment, such as peripheral neuropathy, fatigue, cognitive symptoms, and pain. Younger breast cancer survivors also experience more psychosocial distress than middle-aged and older women, and many report feeling “out of sync” with their friends and peers while having to face the challenges of cancer diagnosis and treatment. The menopause transition and infertility may be important components of this distress. Disruptions in family and marital relationships, concerns about caring for children, work-related difficulties, and insurance and economic issues all add to the burdens of younger survivors. Better psychological adjustment among younger patients has been found to be associated with greater social support, the use of coping strategies, and symptom management [29], and the physical and mental health status of many survivors improves as time from treatment increases. However, younger survivors face more potential years of symptom burden and anxiety about their future. Researchers are learning more about the impact of cancer diagnosis and treatment on the lives of younger adults, but we will need studies following survivors for 10 years or longer to track the type and time course of treatment effects on physical status, psychological status, and quality of life. We also need longitudinal information about male breast cancer survivors and about individuals diagnosed with cancers other than breast cancer. This information will help to inform intervention studies for long-term condition management and mental health care, particu-
larly for patients diagnosed with cancer in their 30s and 40s.

Rural or urban residence. In the United States, disparities in cancer diagnosis, treatment, and mortality have been associated with rural residence [30-32]. In 2013 an estimated 22.4% of North Carolinians resided in rural areas, concentrated in the western and southern areas of the state [33]. Rural communities may lack access to the health care and supportive services necessary to maintain or improve quality of life following a cancer diagnosis. Lack of available services (eg, health clinics, physical therapy, psychotherapy, and nutritional services) may necessitate that cancer survivors drive longer distances to receive care, thus incurring higher transportation and associated costs and/or time off from employment for patients and/or caregivers. Individuals who lack family or other social resources may be particularly at risk. Rural communities may also have a higher prevalence of residents who have low educational attainment, lower incomes, and/or no health insurance [34].

Many studies, but not all, have found significantly poorer mental health among rural cancer survivors than among urban survivors. In the largest study to date, 18.8% of rural survivors in a US population-based sample reported clinically significant psychological distress, compared with 12.8% of urban survivors [35]. Importantly, this pattern does not appear to reflect an underlying difference in the general population, which suggests that observed rural-urban differences among survivors emerge after cancer diagnosis. Routine screening for depression is low regardless of rurality, but rural survivors who need mental health services may face the additional challenge of not finding ready access to health care providers and resources. Developing effective interventions that can be delivered in innovative ways to rural survivors, less mobile patients, and/or those with fewer resources could help to alleviate psychological morbidity among cancer survivors.

Mental Health Screening Recommendations

Psychosocial oncology is a multidisciplinary field that specializes in the psychological, social, and behavioral dimensions of cancer [36]. It has particular relevance for the quality of life of cancer patients from diagnosis through survivorship care, and it can greatly assist in improving the general health status of survivors. Recently, the American Society of Clinical Oncology (ASCO) published adapted guidelines for the screening, assessment, and treatment of anxiety and depressive symptoms in adults with cancer [37]. These guidelines are an excellent resource for recommendations regarding the timing of symptom screening, screening tools, and follow-up care.

In general, periodic mental health screening using validated instruments is recommended across the continuum of cancer care. Widely used screening instruments for depression and/or anxiety that are referenced in the ASCO guidelines include the 9-item Personal Health Questionnaire, the Hospital Anxiety and Depression Scale, the Geriatric Depression Scale, the Beck Depression Inventory, the Center for Epidemiological Studies–Depression Scale, the Spielberger State-Trait Anxiety Inventory, and the Beck Anxiety Inventory. Another relevant screening tool/system is the National Institutes of Health’s Patient Reported Outcomes Measurement and Information System, which has computerized adaptive-testing item banks and brief questionnaire assessment tools [38]. Timely identification and treatment of mental health concerns can greatly improve both the mental and physical health of cancer survivors.

In addition to using psychosocial measures of mental health or general distress, some clinicians may find it useful to have patients complete brief quality-of-life assessments, such as the 12-Item Short-Form Health Survey [39], the Functional Assessment of Cancer Therapy scale—General [40], or a single-item assessment (asking patients to indicate their overall quality of life on a scale from 0 to 10). This can provide another measure of how a patient’s physical or mental health status is affecting his or her overall quality of life, and it may be helpful in evaluating the impact of mental health interventions on the lives of survivors.

Summary

The quality of life of cancer survivors is multifaceted and is influenced by a variety of cancer-related and noncancer factors from the time of cancer diagnosis through long-term survivorship. Physical health and symptoms directly affect mental health, and vice versa. Cancer outcomes—like those of most illnesses—are influenced by socioeconomic status, access to care, supportive services, and rural-urban factors, all of which contribute to the well-being of cancer survivors in North Carolina.

Screening for mental health morbidity is just as important as monitoring physical health among cancer survivors, and mental health screening needs to be better integrated into active cancer treatment and survivorship. We suggest annual mental health screening using the ASCO guidelines described previously, with appropriate referrals to mental health professionals in patients’ communities or surrounding areas. Given that almost 1 in 4 persons in North Carolina live in rural areas and may have lower incomes and/or no health insurance, it will be particularly important to provide assistance through social workers or patient navigators who can identify appropriate and affordable resources to improve patients’ mental health status.

Future research will need to follow survivors long term to identify critical opportunities for follow-up, opportunities for physical and mental health interventions, and factors that might mitigate or buffer the adverse consequences of cancer and treatment. There is also a need for survivorship studies that focus on cancers other than breast cancer, on younger patients, and on male patients.

Michelle J. Naughton, PhD, MPH
professor, Department of Social Sciences and Health Policy, Division of Public Health Sciences, Wake Forest University School of Medicine, Winston-Salem, North Carolina.
References


Cancer in a 29-County Area in Eastern North Carolina: An Opportunity to Reduce Health Inequities

C. Suzanne Lea, Ann King

Cancer mortality rates are higher in a 29-county area of Eastern North Carolina than in the state’s other 71 counties combined; within this 29-county subregion, African Americans have higher cancer mortality rates than whites. Better integration of health promotion and structural changes that improve health care access and delivery are needed to reduce these disparities.

Cancer mortality rates are an indicator of population health and have been continually declining over the past 2 decades in the United States [1]. Despite tremendous progress, deaths from cancer still accounted for 23.3% of all deaths in the United States in 2010 [2], and it is projected that in North Carolina in 2014, a total of 57,298 people will be diagnosed with cancer, and 20,155 people will die from cancer [3]. Cancer deaths thus constitute approximately 22.5% of all deaths in the state, making it the leading cause of death [4]. Nationally, the lifetime probability of being diagnosed with an invasive cancer is higher for men than for women (44% versus 38%), and the risk of cancer varies with age [1]. Cancer incidence and mortality rates also vary by race/ethnicity and geographic region, both nationally and in North Carolina [5].

In this discussion of cancer in Eastern North Carolina, we will focus on a 29-county subregion that is home to approximately 1.5 million of North Carolina’s nearly 10 million residents [6] (see Figure 1). On average, this region has higher unemployment rates and a greater proportion of minority individuals compared with the rest of the state, and residents of this region have lower incomes and lower educational attainment [7, 8]. Of the 40 counties in North Carolina that are most economically distressed, 19 are in this 29-county area [9]. Within the 29-county subregion, several coastal counties have a population that is more affluent than that of the interior coastal plain.

An analysis of mortality data obtained in August 2013 from the North Carolina Central Cancer Registry reveals that, for the years 2006 through 2010, cancer mortality rates for the cancers presented in Table 1 were higher in the 29-county region than in the state’s other 71 counties. The highest mortality rates in both regions were for lung or bronchus cancer, invasive female breast cancer, prostate cancer, and colorectal cancer. Black residents of the 29-county eastern subregion had higher mortality rates than did blacks in the rest of North Carolina, whites in the 29-county subregion, or whites in the rest of the state. The mortality rate from all cancers combined was 16% higher in the 29-county eastern subregion than in the rest of the state, and cervical cancer mortality was 53% higher in the eastern subregion than in the rest of the state. How can a state with such superb cancer research and treatment resources have such inequities in cancer outcomes?

Screening modalities for breast, colorectal, prostate, and cervical cancers allow for early detection of cancer, before symptoms begin. Table 2 provides results from the 2012 Behavioral Risk Factor Surveillance System (BRFSS) survey, which asked respondents about their use of mammography, colonoscopy, prostate-specific antigen (PSA) testing, and Papanicolaou (Pap) smear testing [10]. Respondents living in the 29-county eastern subregion reported similar use of colonoscopy, PSA testing, and Pap smears compared with respondents elsewhere in the state [10].

Behavioral factors that increase the risk of dying from cancer are more common in the 29-county eastern subregion than in the remaining 71 counties of North Carolina. Smoking remains a significant health issue in the eastern subregion, with 36.6% of adults smoking cigarettes daily, compared with 33.04% of adults in the rest of the state [10]. Data from the BRFSS surveys during the period 2005–2009 also showed that 31% of adults were obese in the eastern subregion, compared with 28% of adults in the rest of the state [11].

Geographic Disparities in Cancer Outcomes

Although cancer screening behaviors are relatively similar across North Carolina, cancer mortality rates remain higher in the 29-county eastern subregion, probably as a result of a variety of lifestyle, economic, and social factors that are fundamentally driven by income, poverty, educational attainment, and other social determinants of health.
These factors influence whether individuals seek diagnostic services, treatment, surveillance, and follow-up care. Several factors influence a person’s decision to seek medical care. The Patient Protection and Affordable Care Act of 2010 is expected to provide more Americans with health insurance coverage in the coming years, but broader availability of insurance coverage may not eliminate disparities. Other patient barriers to cancer care include inability to pay for diagnostic screening and treatment due to high copayments, lack of transportation, difficulty obtaining time off from work, fear, distrust, illiteracy, and not wanting to burden family members. One recurring barrier for uninsured individuals is the difficulty of finding a health care provider who will provide low-cost diagnostic services when screening results are positive; this problem is particularly evident for diagnostic screening and treatment of breast and colorectal cancer.

In many parts of Eastern North Carolina, federal and free community clinics have arrangements with local gastroenterology and radiology groups that allow some patients to receive discounted diagnostic screening. Some local foundations also provide screening and treatment support, although it may be limited to residents of certain counties. Although some state programs provide screening, diagnosis, and treatment coverage—such as the North Carolina Breast and Cervical Cancer Control Program—such programs do not meet all of the demand in rural Eastern North Carolina. As a result of this unmet need, patients may eventually present to the emergency department of a local or tertiary care center for diagnosis and linkage into care, which is an expensive option.

Possible Solutions

Although medical professionals may not be able to influence social and economic factors, we certainly can do our best to provide a medical home and coordination of care across the cancer continuum. First, structural and systems improvements in health care are needed. Lay health advisors have been successful in addressing health inequities among lower-income women in Eastern North Carolina, and this model could be expanded to additional federally funded community clinics and local health departments.

Patient navigation can also help to address health care disparities and barriers to care. In cancer care, patient navigation refers to individualized assistance offered to patients, families, and caregivers that helps them overcome health care system barriers and facilitates timely access to high-quality medical and psychosocial care; such assistance can be offered before a cancer diagnosis and throughout all phases of the cancer experience. By 2015 cancer programs accredited by the American College of Surgeon’s Commission on Cancer will be required to implement a patient navigation process. Ideally, a lay health advisor and patient navigator (often a nurse) would provide seamless guidance for patients across the continuum of cancer care. Data will be forthcoming on quality of care, cancer recurrence, and survivorship among patients who receive such guidance.

In addition to structural and systems improvements, health information technology can help to improve coordination of care by integrating care across different systems (such as public health departments, private practices, or academic medical centers and their affiliated practices). Telemedicine and other technologies are also being used to diagnose and treat cancer patients closer to home. For example, expanded integration of cancer services within the local hospital network may reduce patients’ transportation burden by eliminating the need to drive to Greenville (or further) for certain aspects of cancer care. Structural and system improvements may emerge by having a bet-
Table 1: Cancer Mortality Rates for 29 Counties in Eastern North Carolina and for the Rest of the State (71 Counties), by Race, 2006–2010

<table>
<thead>
<tr>
<th>Cancer type</th>
<th>In eastern region</th>
<th>In the rest of the state</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Whites</td>
<td>Blacks</td>
</tr>
<tr>
<td>Lung/bronchus</td>
<td>99.1</td>
<td>77.2</td>
</tr>
<tr>
<td>Breast</td>
<td>37.9</td>
<td>51.1</td>
</tr>
<tr>
<td>Prostate</td>
<td>23.2</td>
<td>56.8</td>
</tr>
<tr>
<td>Colon/rectum</td>
<td>24.8</td>
<td>31.0</td>
</tr>
<tr>
<td>Pancreas</td>
<td>16.7</td>
<td>20.3</td>
</tr>
<tr>
<td>Melanoma</td>
<td>6.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Cervix</td>
<td>3.7</td>
<td>6.3</td>
</tr>
<tr>
<td>All cancers</td>
<td>293.4</td>
<td>308.5</td>
</tr>
</tbody>
</table>

*These 29 counties are shown in Figure 1.
†Invasive ductal carcinoma in women.

Source: Mortality rates for cancer sites by race and region were generated in August 2013 by a statistician at the North Carolina Central Cancer Registry using the mortality rates for 2006–2010.

Table 2: Number and Percentage of North Carolina Survey Respondents Who Reported That They Had Been Screened for Cancer, by Region

<table>
<thead>
<tr>
<th>Type of screening</th>
<th>Region†</th>
<th>No.</th>
<th>% (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mammogram§</td>
<td>Entire state</td>
<td>4,116</td>
<td>75.16 (73.57–76.67)</td>
</tr>
<tr>
<td></td>
<td>Eastern region</td>
<td>586</td>
<td>73.25 (69.19–76.95)</td>
</tr>
<tr>
<td></td>
<td>Rest of state</td>
<td>3,530</td>
<td>75.49 (73.76–77.14)</td>
</tr>
<tr>
<td>Colonoscopy†</td>
<td>Entire state</td>
<td>5,057</td>
<td>70.66 (68.93–71.90)</td>
</tr>
<tr>
<td></td>
<td>Eastern region</td>
<td>696</td>
<td>71.67 (68.01–75.06)</td>
</tr>
<tr>
<td></td>
<td>Rest of state</td>
<td>4,361</td>
<td>70.24 (68.58–71.84)</td>
</tr>
<tr>
<td>PSA test¶</td>
<td>Entire state</td>
<td>2,042</td>
<td>58.85 (56.57–61.09)</td>
</tr>
<tr>
<td></td>
<td>Eastern region</td>
<td>268</td>
<td>63.20 (57.24–68.78)</td>
</tr>
<tr>
<td></td>
<td>Rest of state</td>
<td>1,774</td>
<td>58.16 (55.69–60.59)</td>
</tr>
<tr>
<td>Pap smear§</td>
<td>Entire state</td>
<td>3,736</td>
<td>81.54 (79.97–83.01)</td>
</tr>
<tr>
<td></td>
<td>Eastern region</td>
<td>529</td>
<td>82.12 (78.14–85.51)</td>
</tr>
<tr>
<td></td>
<td>Rest of state</td>
<td>3,207</td>
<td>81.44 (79.72–83.05)</td>
</tr>
</tbody>
</table>

Note. CI, confidence interval; Pap, Papanicolaou; PSA, prostate-specific antigen.
†The eastern region is the 29-county area in Eastern North Carolina depicted in Figure 1.
‡Includes women aged 40 years or older who answered yes to the question “Have you had a mammogram within the past 2 years?”
§Includes men and women aged 50 years or older who answered yes to the question “Have you ever had a colonoscopy?”
¶Includes men aged 40 years or older who answered yes to the question “Have you ever had a prostate specific antigen (PSA) test?”
| It is predicted that by the year 2030 the number of new cases of cancer diagnosed each year in the United States will have increased by 45% (from 1.6 million to 2.3 million), largely as a result of aging; by 2022 the number of cancer survivors will have increased from 13.7 million to nearly 18 million [19]. Moving forward, multimodal strategic programs focusing on prevention must be integrated into cancer care. We have an opportunity to focus on minority populations in rural areas, as this is where we can have the greatest impact on cancer mortality.

Behavioral changes are also needed to help reduce cancer disparities. Cancer prevention and control strategies hinge on effective application of knowledge about human behavior [16]. Because smoking prevalence is high in Eastern North Carolina, smoking cessation and prevention are important public health initiatives—not just for cancer but also for many chronic diseases. North Carolina’s Tobacco Prevention and Control Branch offers many strategies for smoking cessation [17], and the branch provides information on smoking cessation resources around the state.

Obesity in rural Eastern North Carolina also remains a challenge due to a variety of cultural, geographic, social, and economic factors. In addition, emerging evidence suggests that interactions of health behaviors are related to cancer progression [16]. Recognizing that obesity has economic effects on our state, North Carolina leaders have promoted the Eat Smart, Move More initiative, which aims to increase the number of North Carolinians who are maintaining a healthy weight. This program focuses on promoting breast feeding, increasing physical activity in schools, building structural access to fruits and vegetables, and promoting work-site wellness [18]. Innovations in mobile technology to promote smoking cessation and exercise are also being tested.

Finally, there are many examples across the state of individuals and local community partnerships promoting healthy choices. For example, the faith-based community has been engaged in reducing the burden of diabetes and heart disease in Eastern North Carolina, and outreach for cancer prevention could be enhanced using these models.

Conclusion

It is predicted that by the year 2030 the number of new cases of cancer diagnosed each year in the United States will have increased by 45% (from 1.6 million to 2.3 million), largely as a result of aging; by 2022 the number of cancer survivors will have increased from 13.7 million to nearly 18 million [19]. Moving forward, multimodal strategic programs focusing on prevention must be integrated into cancer care.
health care practices. Just providing education regarding risks is ineffective for effecting behavioral change. As health care providers, we need to lead the population toward healthy lifestyle choices by encouraging smoking prevention and cessation; a diet that includes plenty of vegetables, fruits, and whole grains; healthy weight management; physical activity; use of sunscreen; and stress management. Health promotion should be the cornerstone of health care systems and community action, and it should aim to reduce cancer risks by fostering self-efficacy and positive health choices.

The unfortunate reality is that ethnic and racial minorities in Eastern North Carolina do not experience optimal health. Because the cancer burden is greatest in this part of the state, access to high-quality care centered on optimizing survivorship should be a primary goal of the health care system. This goal must be recognized as a priority both in statewide policy making and in public health and health care planning.

C. Suzanne Lea, PhD associate professor, Epidemiology, Department of Public Health, Brody School of Medicine, East Carolina University, Greenville, North Carolina.
Ann King, DNP, FNP-BC clinical associate professor, Doctor of Nursing Practice Program, Adult Geriatric and Family Nurse Practitioner Concentrations, College of Nursing, East Carolina University, Greenville, North Carolina.

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References
Running the Numbers

A Periodic Feature to Inform North Carolina Health Care Professionals About Current Topics in Health Statistics

Gynecologic Cancers:
Incidence and Mortality Trends Among Women in North Carolina

This analysis used data on gynecologic cancers among women in North Carolina obtained from the North Carolina Central Cancer Registry (NCCCR). The NCCCR collects, processes, and analyzes data on all cancer cases diagnosed among North Carolina residents. All health care providers who diagnose or treat cancer are required to report cases to the NCCCR within 6 months of diagnosis. To examine trends in incidence and mortality, annual incidence and mortality rates were calculated for gynecologic cancers among women in North Carolina (age-adjusted to the 2000 US standard population) for the years 1995 through 2011 (the most recent year for which complete incidence data were available).

According to the Centers for Disease Control and Prevention (CDC), there are 5 main types of gynecologic cancers: cervical, uterine, ovarian, vaginal, and vulvar. The cancer site groupings were defined according to site recode variables from the Surveillance, Epidemiology, and End Results (SEER) Program of the National Cancer Institute [1]. When calculating rates for minority women, we included all races other than white. These cancers do not include in-situ cases.

Cervical Cancer

Cervical cancer, which is primarily caused by human papillomavirus (HPV) infection, can be prevented through regular Papanicoloau (Pap) smear screenings and use of the recently developed HPV vaccine [2]. The incidence rate of cervical cancer among all women in North Carolina decreased slightly between 1995 and 2011, from 9.4 to 7.3 cases per 100,000 women (Figure 1). During that same period, the rate of mortality from cervical cancer also decreased, from 3.6 to 1.9 deaths per 100,000 women (Figure 2). The incidence rates for white and minority women differed throughout this period, with minority women consistently having higher cervical cancer incidence rates than white women. The incidence rate among white women remained stable between 1995 and 2011 (Figure 3), but the incidence rate among minority women decreased significantly, from 14.0 to 7.8 cases per 100,000 minority women (Figure 4). Similarly, the mortality rate among white women remained stable (Figure 5), while a significant decrease occurred among minority women, from 7.7 to 2.6 deaths per 100,000 minority women (Figure 6). The disparity in mortality rates between whites and minorities was significant over those years.

Uterine Cancer

To calculate rates for uterine cancer, this analysis included endometrial cancer, which is cancer of the lining of the uterus (corpus uteri), and cancer of the uterus not otherwise specified. The incidence rate of uterine cancer among all women in North Carolina increased steadily between 1995 and 2011 (Figure 1), from 21.2 to 24.4 cases per 100,000 women. Nevertheless, the mortality rate remained stable from 1995 through 2011 (Figure 2). There is no standard or routine method of screening for endometrial cancers, but they are usually detected at early stages through symptoms and can be treated effectively [3]. Although the incidence rate of uterine cancer was initially lower among minority women than among white women, the rate among white women increased only slightly between 1995 and 2011 (Figure 3), while the rate among minority women increased significantly, from 17.9 to 25.5
cases per 100,000 minority women (Figure 4). The mortality rates among both white women (Figure 5) and minority women (Figure 6) remained stable over those years.

**Ovarian Cancer**

The incidence rate of ovarian cancer among all women in North Carolina remained stable from 1995 to 2011 (Figure 1), while the rate of mortality from ovarian cancer decreased slightly between 2002 and 2011 (Figure 2). As is the case for endometrial cancers, ovarian cancers cannot be detected through routine screening tests. The incidence rates for ovarian cancer among both white women (Figure 3) and minority women (Figure 4) remained stable between 1995 and 2011. Rates of mortality from ovarian cancer among both groups decreased slightly during those years: from 8.8 to 7.5 deaths per 100,000 among white women (Figure 5), and from 8.2 to 6.7 deaths per 100,000 among minority women (Figure 6).

**Vaginal Cancer**

Vaginal cancer is rare and is known to be caused by HPV infection [4]. The incidence rate of vaginal cancer among all women in North Carolina was low and remained stable between 1995 and 2011 (Figure 1). The rate of mortality from vaginal cancer was also low and remained stable from 1995 to 2011 (Figure 2). The incidence rate of vaginal cancer among white women remained stable from 1995 to 2011 (Figure 3), while the rate among minority women initially remained stable and then increased slightly, from 0.9 to 1.3 cases per 100,000 minority women (Figure 4). The rate of mortality from vaginal cancer remained stable among white women (Figure 5) while decreasing slightly among minority women (Figure 6).
Vulvar Cancer

Vulvar cancer is another rare cancer known to be caused by HPV infection [4]. Incidence and mortality rates for vulvar cancer among all women in North Carolina remained steady from 1995 to 2011 (Figures 1 and 2). The incidence rates among minority women (Figure 4) were consistently lower than the incidence rates among white women (Figure 3), but rates were stable for both groups from 1995 through 2011. The rate of mortality from vulvar cancer also remained stable from 1995 to 2011 for both white women (Figure 5) and minority women (Figure 6).

Conclusion

Overall, the incidence rates of ovarian, vaginal, and vulvar cancers remained stable between 1995 and 2011, and there was a slight decrease in the incidence of cervical cancer. However, there was a slight increasing trend in the incidence of uterine cancer. The rates of mortality from uterine, vaginal, and vulvar cancers remained stable between 1995 and 2011, while rates of mortality from ovarian and cervical cancer decreased slightly. This finding suggests that treatments can be effective if these cancers are detected at early stages. Looking at incidence and mortality trends by race illustrates disparities between white women and minority women; identifying such disparities can assist cancer control programs in directing activities to the groups in need of additional prevention and treatment efforts.

Several gynecologic cancers are caused by HPV infection and thus could be largely prevented by appropriate vaccination strategies. The Advisory Committee on Immunization Practices of the CDC recommends HPV vaccination for females aged 11 or 12 years of age (or up to age 26 years, if not previously vaccinated) [5]. Pap screening is also recommended for all women aged 21–65 years [6].

**FIGURE 3.**

**FIGURE 4.**
Finally, as treatments are effective for most gynecologic cancers when they are detected at early stages, routine physical exams and screening are recommended for all women. NCJM


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References

Philanthropy Profile

The V Foundation’s Efforts to Support Cancer Research

Cancer therapies have improved remarkably in recent decades, thanks to the ongoing work of dedicated researchers worldwide. As the home of several strong research programs—including the Duke Cancer Institute, the Comprehensive Cancer Center of Wake Forest University, and the Lineberger Comprehensive Cancer Center at the University of North Carolina (UNC)—North Carolina remains an active hub for this research, in part due to the funding of various philanthropic organizations.

One of these organizations is The V Foundation for Cancer Research, which was founded by ESPN and Jim Valvano, the men’s head basketball coach at NC State University from 1980 to 1990. In 1993 Valvano announced that he would be partnering with ESPN to start a foundation with a mission to find cures for cancer through supporting the most promising cancer research. Valvano had been diagnosed with cancer at the age of 46 years, and he died soon after his announcement. Nevertheless, through the support of his friends, family, and the nation, The V Foundation has made significant contributions to the field of cancer research over the past 20 years. From 1994 to 2013, The V Foundation awarded $115 million in grants to cancer research, $13 million of which was awarded to cancer researchers in North Carolina.

The V Foundation’s Unique Philanthropic Model

Unlike other cancer advocacy organizations and foundations, The V Foundation awards 100% of direct cash donations to cancer research. Thanks to an endowment that covers all operating expenses, The V Foundation is able to use donations for the intended purpose of furthering cancer research. In addition, The V Foundation has chosen to fund cancer research across all organ types. This strategy not only allows for the flexibility to fund preeminent research regardless of organ type, but it also furthers research among cancer types that are traditionally less well funded. Finally, The V Foundation allows only 1 applicant per institution for its V Scholar and Translational grants. This policy encourages institutions to have an internal competition to determine which grant applications should be submitted; thus the review committee considers only the leading research from any given institution.

All of the submitted grant applications are reviewed by The V Foundation’s Scientific Advisory Committee, which is comprised of national leaders in medicine and science who specialize in major areas of cancer research. This committee also has 2 lay community members who participate in the grant selection process. These members were recommended to The V Foundation for their personal experience with cancer and/or their advocacy efforts in the field.

The V Foundation awards 3 types of grants: V Scholar grants, Translational grants, and Designated grants. V Scholar grants were established to meet the initial vision of the organization, which was to support promising young researchers and to help them establish their careers. (Now more than ever, when larger funding streams such as the National Institutes of Health have been stagnating, V Scholar grants provide a means for young researchers to establish themselves so that they can qualify for larger grants in the future.) Translational grants are intended to accelerate the process of bringing research from the laboratory to the patient. Finally, Designated grants are inspired by particular areas of scientific interest and/or geographic reach. They are selected on the basis of scientific merit as determined by the Scientific Advisory Committee.

Recent Grant Recipients in North Carolina

Gang “Greg” Wang, PhD, a researcher at the UNC Lineberger Comprehensive Cancer Center, is a recent V Scholar grant recipient. Wang’s research focuses on DNA-modifying enzymes that are often abnormally...
expressed, mutated, and/or hyperactivated among various forms of blood malignancies. His research specifically focuses on mutations in a gene that encodes an enzyme that accounts for 10%–20% of certain types of lymphomas. By identifying the relationship between this gene and other biochem-icals, Wang has been able to identify key interacting factors that could respond to pharmacological manipulation.

Another V Foundation award recipient is Kim Rathmell, MD, PhD, who is a researcher at the UNC Lineberger Comprehensive Cancer Center. She recently received a Translational grant for her research regarding mutations that affect DNA packaging in clear cell renal cell carcinoma (ccRCC). Her 3-part project aims to understand the global impact of these mutations on the way DNA is organized in affected tumors, to explore how changes promote cancer growth, and to test drugs to selectively kill cancer cells that harbor these changes. In the first year of research, Rathmell’s team discovered that tumors with mutations in a key gene have DNA that is unwound across large portions of the genome, which allows for activation of many target genes associated with ccRCC.

Finally, John Cavanagh, PhD, was recently awarded a V Foundation Designated grant for his work with the Jimmy V–NC State Cancer Therapeutics Training Program. This program, which is based at NC State University, supports young researchers from high school through undergraduate who work in various cancer research laboratories. Researchers in this program discovered a class of molecules with antibacterial properties that appear to enhance the effects of novel anticancer agents. To follow up on this discovery, more than 1,000 molecules are now being screened in combination with anticancer agents to determine their effectiveness in various cancer cell lines.

The V Foundation’s Impact in North Carolina

Since its inception, The V Foundation has awarded 54 grants to researchers in North Carolina. These grants have supported promising young researchers and have allowed for preeminent research to transition more quickly from the lab to the bedside. Although The V Foundation supports cancer research nationwide, North Carolina’s cancer research institutions have remained competitive in securing these grants. Moving forward, The V Foundation is identifying areas of cancer research that are in need of additional funding, including research focused on the immune system and research related to pediatric cancer. Additionally, The V Foundation is looking to allocate more resources towards understanding how bioinformatics can inform biomedical research.
Here’s what happened...

My story may help you.

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It turned out I had ovarian and uterine cancers. Getting diagnosed and treated wasn’t easy. But now my doctor and I are optimistic about my future.

Please listen to your body. If something doesn’t feel normal for two weeks or longer, see your doctor.”

– Jennie M., Washington, D.C.

Gynecologic cancer includes cervical, ovarian, uterine, vaginal, and vulvar cancers. Signs and symptoms are not the same for everybody...so get the facts.

Get the Inside Knowledge. Get the facts about gynecologic cancer.

www.cdc.gov/cancer/knowledge  1-800-CDC-INFO
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Jason Coleman
Clinical Support Specialist
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Justin Cooler
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