ARTICLE TITLE: Cancer Screening, Prevention, and Treatment in People With Mental Illness

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After reading the article “Cancer Screening, Prevention, and Treatment in People With Mental Illness,” the learner should be able to:
1. Describe the factors in the theoretical framework used to describe the incidence of cancer deaths in people with mental illness.
2. Describe interventions intended to decrease cancer risk in people with mental illness.
3. Review recommendations for prevention, screening, and early detection of cancer in people with mental illness.

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People with mental illness die decades earlier in the United States compared with the general population. Most of this disparity is related to preventable and treatable chronic conditions, with many studies finding cancer as the second leading cause of death. Individual lifestyle factors, such as smoking or limited adherence to treatment, are often cited as highly significant issues in shaping risk among persons with mental illness. However, many contextual or systems-level factors exacerbate these individual factors and may fundamentally drive health disparities among people with mental illness. The authors conducted an integrative review to summarize the empirical literature on cancer prevention, screening, and treatment for people with mental illness. Although multiple interventions are being developed and tested to address tobacco dependence and obesity in these populations, the evidence for effectiveness is quite limited, and essentially all prevention interventions focus at the individual level. This review identified only one published article describing evidence-based interventions to promote cancer screening and improve cancer treatment in people with mental illness. On the basis of a literature review and the experience and expertise of the authors, each section in this article concludes with suggestions at the individual, interpersonal, organizational, community, and policy levels that may improve cancer prevention, screening, and treatment in people with mental illness. CA Cancer J Clin 2016;66:133-151. © 2015 American Cancer Society.

Keywords: epidemiology, health disparities, prevention, screening and early detection

Introduction

Mental Illness and Health Disparities

Despite the high prevalence of mental illness among adults, only in the last decade has this population been recognized as experiencing significant health disparities, including increased morbidity and mortality. Mental illness is exceedingly common, with Substance Abuse and Mental Health Service Administration statistics indicating that almost 44 million adults (18.6%) had any mental illness in the last year, and that, of those, almost 10 million (4.1%) had a serious mental illness (SMI). Individuals with SMI—defined as a mental illness like schizophrenia or bipolar disorder that results in substantial functional impairment—are particularly likely to experience significantly reduced life expectancy. A report by Parks et al raised national awareness by stating that people with SMI die decades earlier in our country compared with the general population. Most of this disparity is related to preventable and treatable chronic conditions, such as cardiovascular disease and cancer, with studies finding that, similar to the general population, cancer is the second leading cause of death. Multiple factors contribute to this excess morbidity and mortality, including behavioral and lifestyle factors,
socioenvironmental circumstances, and access to and quality of medical care. However, more attention has been focused on promoting change on an individual level, and there has been less emphasis on the contextual inequities (eg, food environments, poverty, discrimination) that drive many of these disparities.10,11

Mental Illness and Cancer

The evidence to date from epidemiologic studies regarding mental illness and cancer is now abundant, complex, and conflicting. Reports regarding cancer incidence are particularly inconsistent, with studies finding the risk of cancer among individuals with mental illness to be higher, lower, or equivalent to that of the general population.12-30 A recent study comparing a state Medicaid SMI cohort with the general US population revealed that total cancer incidence was 2.6 times higher in the SMI cohort.22 In contrast, studies like that by Ji et al, who reviewed a large cohort of Swedish people with schizophrenia and their first-degree relatives, found an overall decreased incidence rate of cancer in both people with schizophrenia and their first-degree relatives.18 Adding to this complexity, findings tend to differ (but not necessarily in consistent directions), depending on whether studies control for behavioral risk factors, such as smoking, or whether they stratify by sex. For example, even within single psychiatric diagnostic categories, cancer risk patterns vary, with researchers noting that it is possible that schizophrenia serves as a protective factor for cancer15,17,24,25 as well as a risk.23 Indeed, comparing studies with differing approaches to controlling for confounding serves to highlight the critical impact of multiple behavioral and environmental risk factors in this population. In reality, the very issue of health disparities in this population is most likely because of the prevalence of modifiable risk factors.7,9 A deeper understanding of the upstream contribution to these risk factors provides the opportunity to develop more effective interventions and reduce health disparities.

Overall, studies of incidence vary widely along many dimensions. This provides a multitude of rich data but exacerbates the lack of consensus regarding the link between mental illness and cancer incidence, leading some researchers to conclude that "the epidemiological puzzle remains unsolved."29 Others, however, suggest that higher quality studies (reflected by larger study samples, greater numbers of overall cases, and longitudinal data with higher person-years of follow-up) provide a more consistent picture of higher risk, for example, the greater risk of breast cancer among patients with schizophrenia.31 Nevertheless, studies consistently find that cancer accounts for much of the disease burden of individuals with mental illness. For example, a large prospective study of patients with schizophrenia revealed an all-cause death rate nearly 4 times higher than that in the general population, with cancer as the second most common cause of death after suicide and before cardiovascular disease.8

In contrast to the cancer incidence findings, many recent studies report increased cancer mortality rates in people with mental illness.8,32-34 Although the evidence is not unequivocal, findings more consistently point to a higher standardized mortality ratio within SMI populations.8,35,36 Various factors may contribute to higher mortality, including more advanced stage at presentation because of delayed diagnosis, comorbidities that complicate treatment (including psychotropic and oncology drug interactions), poorer quality care, and reduced access to specialized treatment.37

Although individual lifestyle factors, such as smoking or poor adherence to treatment, play a significant role in shaping risk among persons with mental illness, many contextual or systems-level factors exacerbate these individual factors. These contextual factors, including lack of integration between mental health and medical care systems (as well as the complexity of navigating them), mental illness stigma and physician bias, as well as social circumstances (eg, lower education, income, and social integration; greater unemployment, homelessness, and overall poorer quality housing and neighborhoods),1,2,5 may fundamentally drive health disparities among people with SMI. If it indeed were the situation that cancer incidence was no greater in people with SMI, but case fatality was higher, then the higher prevalence of commonly known cancer risk factors, such as tobacco use and obesity, would be less likely to explain the higher mortality rates.38 This multitude of factors contributing to cancer risk among people with SMI presents a research and clinical challenge, but it also presents multiple opportunities for intervention as well as a call to action. This underserved and vulnerable population confronts a particularly challenging set of obstacles to receiving high-quality care for all diseases, including cancer. Both understanding and modifying the risk of cancer in people with SMI and overcoming barriers to care define important public health and social justice goals. The objectives of this review were to evaluate and synthesize the available data on the prevention, screening, and treatment of cancer in people with SMI; to provide further reconceptualization of this complex topic; and to provide a pragmatic approach to clinical care. We propose a modification of the ecological model as the underlying theoretical framework for this review to highlight the multiple contributing factors and points of intervention.

Theoretical Framework

There are many “ecological models” or multilevel frameworks designed to explicate the multiple levels that can affect health and health behavior.39-41 To a certain extent, these models arose in response to interventions focused at the
individual level, which conceptualized health as largely determined by individual characteristics or attributes, with individuals bearing primary responsibility for health outcomes. These individual-level interventions have been criticized by some as “blaming the victim” and can be particularly problematic for marginalized and stigmatized populations, such as those with experiences of mental illness, because they often fail to acknowledge the overwhelming environmental and societal barriers to good health.

McLeroy et al are generally credited with the development of the well known “social ecological model” in their seminal piece, “An Ecological Perspective on Health Promotion Programs” (although McLeroy himself did not use the term “social ecological model”). As originally articulated, the McLeroy et al social ecological model views health behavior as being determined on 5 levels: 1) intra-personal factors—characteristics of the individual, such as knowledge, attitudes, behavior, self-concept, skills, etc (this includes the developmental history of the individual); 2) interpersonal processes and primary groups—formal and informal social network and social support systems, including the family, work group, and friendship networks; 3) institutional factors—social institutions with organizational characteristics and formal (and informal) rules and regulations for operation; 4) community factors—relationships among organizations, institutions, and informal networks within defined boundaries; and 5) public policy—local, state, and national laws and policies.

As demonstrated by epidemiological studies, cancer incidence and outcomes can be affected on many levels by competing factors. Some factors, such as genetics, have been theorized to either increase or decrease the risk of cancer in people with schizophrenia. Similarly, antipsychotic medications may have antitumor properties, but they may also contribute to the risk of tumors like breast and endometrial cancers, which are hormonally regulated.

By using this multilevel framework (Fig. 1), this article reviews cancer prevention, screening, and treatment among populations with mental illness, with special emphasis on disparities and potential underlying mechanisms. Each section concludes with recommendations for clinical practice in each area. In addition, Table 1 provides a summary of key recommendations for medical clinicians to improve cancer prevention screening and treatment in people with mental illness. The following synthesis demonstrates that the evidence supporting effective interventions is quite limited. Therefore, the clinical practice recommendations are based
on a combination of evidence and the experience and expertise of the authors.

Materials and Methods
We conducted an integrative review to summarize the empirical literature on cancer prevention, screening, and treatment for people with mental illness. An integrative review differs from meta-analyses and systematic reviews, which generally combine evidence from a group of studies using a statistical or quasi-statistical approach to answer a particular question. Integrative reviews summarize evidence from studies with diverse methodologies (eg, experimental and nonexperimental studies) to synthesize the state of the science in a specific topic to guide evidence-based care.46,47 The topic of this review is broad, and there is a significant lack of randomized controlled trials (RCTs), especially in screening and treatment. Because of the complex issues facing the population and the clinicians who care for them, an integrative review provides a unique opportunity to synthesize multiple levels of evidence and opinion to provide practical guidelines for approaching these issues.

Description of Search Strategy
An experienced research librarian assisted L.C.W. and K.E.H. in developing a list of terms and Medical Subject Headings (MeSH terms) that were searched in the following databases: 1) PubMed, 2) Scopus, 3) the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and 4) PsychINFO. Table 2 lists the search terms and limits for each database. We searched for articles that were published between 2005 and 2015 to coincide with the Substance Abuse and Mental Health Service Administration’s (SAMSHA) national call to action to improve health and wellness in people with mental health and substance abuse disorders.48 We considered all study designs (including experimental, quasi-experimental, nonexperimental, and qualitative studies), editorials, and reports. However, to be included in the review, articles needed to have a specific focus on populations whose mental illness preceded the diagnosis of cancer. We excluded case reports, articles focusing only on cancer survivors, and articles that did not clearly specify premorbid psychiatric disease. To simplify the search strategy, we conducted separate searches for “prevention,” “screening,” and “treatment.” Search terms and results are shown in Table 2.

We also undertook hand searches of reference lists from relevant literature reviews. In total, 82 articles were identified using this approach. Three authors (L.C.W., A.S., and A.T.C. reviewed articles and systematically abstracted article information into databases that summarized data collection and methods, sample and setting, results/data, and conclusions. Most of the articles reviewed were cross-sectional studies (34%), RCTs (18%), or nonsystematic reviews (11%) (Table 3; for an expanded version of Table 3, see Supporting Information Tables 1-3 [see online supporting information]).37,43,49-54,56-59,61-130

Synthesis of Findings
Prevention and Risk Factors
This section reviews interventions intended to decrease cancer risk in people with mental illness, with a specific

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**TABLE 1. Key Recommendations for Medical Clinicians to Improve Cancer Prevention, Screening, and Treatment in People With Mental Illness**

| Prevention: Addressing obesity and tobacco use |
|------------------------------------------------|
| Strongly consider metformin for weight loss in people with schizophrenia and obesity or rapid weight gain |
| Actively address tobacco dependence in all people with mental illness, and consider bupropion and varenicline in psychiatrically stable patients |

| Screening |
|-----------|
| Provide a community health worker or peer counselor to help the patient navigate the screening process |
| Increase awareness of cancer screening in mental health service providers |

| Treatment |
|-----------|
| Consciously avoid the tendency toward “diagnostic overshadowing,” or attributing physical symptoms that may indicate cancer to the patient’s mental illness |
| Involve staff from community-based social support, who often have long-term relationships with patients, early in the diagnostic and treatment process |
| Engage people with mental illness in end-of-life treatment decisions |

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**TABLE 2. Example of Search Terms Using PubMed Medical Subject Term (MeSH) Terms**

| Prevention/risk factors |
|-------------------------|
| Schizophrenia, disorders with psychotic features, mood disorders, neoplasm, prevent*, chemoprevent*, chemoprophylaxis*, “prevention and control,” risk factors |

| Prevention/tobacco cessation |
|-----------------------------|
| Schizophrenia, disorders with psychotic features, mood disorders, neoplasm, tobacco use cessation |

| Prevention/weight management |
|-----------------------------|
| Schizophrenia, disorders with psychotic features, mood disorders, neoplasm, prevent*, “prevention and control,” exercise, overweight, body weight changes |

| Screening |
|-----------|
| Schizophrenia, disorders with psychotic features, mood disorders, neoplasm, “early detection of cancer,” “cancer early detection,” “cancer screening,” “cancer early diagnosis,” Papanicolaou test, mammography, colonoscopy |

| Treatment |
|-----------|
| Schizophrenia, disorders with psychotic features, mood disorders, neoplasm, treat*, “clinical trial,” “random allocation,” “randomized controlled trial,” “antineoplastic protocol,” “cancer treatment protocol,” “antineoplastic combined chemotherapy protocols” |
focus on overweight/obesity and tobacco use, which are leading causes of cancer cases in this population. Up to one-third of cancer cases in economically developed countries are related to overweight or obesity, physical inactivity, and/or poor nutrition. People with a current mental illness are almost twice as likely to be obese compared with those without a mental illness. An exacerbating factor is that up to 80% of people taking antipsychotic medication experience antipsychotic induced weight gain. Furthermore, mainstream weight loss interventions often do not address the numerous challenges faced by this population, including limited financial and social resources and stigma.

Similarly, lung cancer is the leading cause of cancer mortality in the United States, and tobacco use accounts for at least 70% of all lung cancer deaths and at least 30% of all cancer deaths. People with a current mental illness are more than twice as likely to smoke cigarettes compared with those without a mental illness. Prevalence estimates for smoking range from 70% to 85% for people with schizophrenia and from 50% to 70% for people with bipolar disorder. In addition, people with schizophrenia smoke more heavily, have more severe nicotine dependence, and have lower quit rates compared with the general population. Smoking disparities are also evident in rates of quitting tobacco use, and an analysis of smoking trends from 2004 to 2011 indicated that smoking rates declined very minimally among people with mental illness.

The underlying causes for higher rates of obesity and tobacco use in people with mental illness are complex and interact on multiple levels. Among them are exposure to chronic stressors (eg, stressful living environments triggering tobacco use and unhealthy eating habits), few financial resources (eg, difficulties paying for tobacco treatment interventions or healthy food options), medication side effects (eg, directly leading to weight gain or triggering tobacco use to mask side effects), and “therapeutic nihilism” (eg, providers’ doubting individuals’ abilities to engage in behavior change). Recognizing these alarming statistics, a significant number of obesity treatment/prevention and tobacco-cessation interventions are being tested in populations with SMI.

**Obesity-Related Interventions**

In 2006, the National Institute of Mental Health released a meeting report which concluded that empirically based interventions to address obesity in people with mental illness were not receiving adequate research attention. Since that time, many studies have been conducted on this topic. Interventions addressing obesity among persons with mental illness concentrate on 2 approaches: general interventions to promote weight loss as well as interventions to reduce antipsychotic use weight gain. These interventions can be behavioral, pharmacological, or both.

There have been at least 8 systematic reviews in the last decade looking at behavioral interventions to promote weight loss in people with SMI, including a recent Cochrane review. For the most part, these interventions consisted of group or individually based programs promoting changes in diet and/or physical activity without elements of cognitive and/or behavioral modification. All reviews noted issues with study design, methodological rigor, and reporting of statistically significant, but clinically insignificant weight loss (ie, less than 5%-7% of initial weight). A notable exception is the 18-month tailored behavioral weight-loss intervention in adults with SMI by Daumit and colleagues, who reported that 37.8% of people in the intervention group achieved statistically and clinically significant weight loss compared with 22.7% of those in the control group (P = .009). That study was unique, in that the weight loss program lasted for 18 months, whereas the programs in other trials generally lasted for less than 6 months. On the basis of their results, the authors hypothesized that persons with serious mental illness take longer than those without serious mental illness to engage in an intervention and make requisite behavioral changes.

Similarly, Bartels and Desilets noted in their review that more successful programs tended to be of longer duration and included both education-based and activity-based approaches, similar to findings in the general population.

The data regarding use of pharmacological agents for weight loss or prevention of weight loss, particularly metformin, are similarly limited. A recent RCT in the Veterans Administration health system found that metformin was modestly effective in reducing weight in clinically stable, overweight outpatients with chronic schizophrenia or schizoaffective disorder over 16 weeks. Like many other studies, however, it showed statistically significant weight loss but not clinically significant weight loss, although findings suggested that the benefits of metformin may continue with longer treatment. On a more encouraging note, an RCT by Wu et al specifically targeted weight gain in the context of first-episode psychosis. Significantly fewer patients in the olanzapine plus metformin group increased their baseline weight by greater than 7%, which was the cutoff for clinically meaningful weight gain, compared with patients in the olanzapine plus placebo group. That study and other studies in the general population suggest that metformin maybe more effective in younger populations.

Given these findings, Hasnain et al concluded in their 2011 review that metformin therapy should be considered in 3 high-risk groups: 1) obese patients with schizophrenia and evidence of glucose dysregulation, irrespective of antipsychotic drug treatment; 2) obese patients with schizophrenia and without current evidence of glucose dysregulation but with a strong family history of diabetes; and 3) young...
| PREVENTION TARGET/PRIMARY AUTHOR | MH DX | STUDY DESIGN | DATA COLLECTION/METHODS | SAMPLE AND SETTING | RESULTS/DATA | CONCLUSIONS |
|----------------------------------|-------|--------------|-------------------------|-------------------|--------------|-------------|
| Tobacco use/van der Meer 2013⁴⁹ | D     | SRMA         | Review of the effectiveness of smoking-cessation interventions in smokers with current or past depression | 49 RCTs           | Adding psychosocial mood management to a standard smoking-cessation intervention increased cessation rates for individuals with past and current depression (11 trials: N = 1844; RR, 1.47; 95% CI, 1.13–1.92; 13 trials: N = 1496; RR, 1.41; 95% CI, 1.13–1.77); bupropion may also significantly increase long-term cessation for smokers with a past history of depression (4 trials: N = 404; RR, 2.04; 95% CI, 1.31–3.18) | Adding a psychosocial mood-management component to a standard smoking-cessation intervention increases long-term cessation rates in smokers with both current and past depression, and bupropion may increase long-term cessation in smokers with past depression |
| Tobacco use/Gibbons & Mann 2013⁵⁰ | M     | MA           | Analysis of RCTs        | N = 8822 patients from 17 studies | Varenicline did not increase rates of suicidal events, depression, or aggression/agitation; it increased the abstinence rate by 124% compared with placebo and by 22% compared with bupropion | The evidence supports the superior efficacy of varenicline compared with placebo or bupropion, without associated NAEs |
| Weight/Bartels 2015⁵¹           | M     | RCT          | Trial of “In SHAPE program,” 12-mo behavioral intervention with fitness club membership and health-promotion coach | N = 211 people with SMI and BMI ≥25 kg/m² in 3 CMHCs in Boston | At 12 mo, intervention participants had significantly greater reductions in weight (P = .029), greater distance on the walk test (P = .037), decreases in BMI (P = .034) and waist circumference (P = .022), and increases in exercise min (P = .01) and physical activity scores (P = .006); improvements were maintained at 18 mo | Demonstrates that health coaching results in overweight and obese adults with SMI achieving and sustaining clinically significant reductions in cardiovascular risk |
| Weight/Daumit et al. 2013⁵²      | M     | RCT          | Trial of 18-mo behavioral weight loss program for adults with SMI | N = 291 participants in 10 outpatient psych programs in central Maryland | In the intervention group, 37.8% lost 5% or more body weight compared with 22.7% in the control group (P = .009) | The program significantly reduced weight in overweight and obese adults with SMI |
| Weight/Hasnain 2011⁵³           | S     | Review       | Literature review on use of metformin for antipsychotic drug-induced weight gain and glucose dysregulation | Twelve trials and 7 reviews/meta-analyses | The literature is encouraging on the effectiveness of metformin for weight gain prevention and treatment; increased age and duration of exposure to antipsychotic treatment reduce metformin’s weight loss effects | Metformin therapy should be considered in all obese schizophrenia patients who have evidence of glucose dysregulation |
| CANCER TYPE/ PRIMARY AUTHOR | MH DX | STUDY DESIGN | DATA COLLECTION/METHODS | SAMPLE AND SETTING | RESULTS/DATA | CONCLUSIONS |
|-----------------------------|-------|--------------|-------------------------|-------------------|--------------|-------------|
| Breast/Mitchell 201454      | M     | SRMA         | Review of literature examining whether women with a mental illness are less likely to receive mammography screening | Multiple          | Significantly reduced rates of mammography screening in women with mental illness (OR, 0.71; 95% CI, 0.66–0.77), mood disorders (OR, 0.83; 95% CI, 0.76–0.90), and particularly SMI (OR, 0.54; 95% CI, 0.45–0.65) | Mammmography rates are lower in women with mental illness, especially SMI |
| Breast, cervical/ Aggarwal 201355 | M     | SR          | Systematic review of health disparities in breast and cervical cancer screening among women with mental illness | Multiple studies  | In total, 19 studies were included; the most commonly discussed facilitator was a relationship with a primary care physician | Breast and cervical cancer disparities persist among women with chronic mental illness, although this population is complex and diverse |
| Breast, cervical, colon/ Happell 201226 | M     | Review      | Narrative review to examine disparities in preventive health care for cancer and infectious diseases among individuals with SMI | Multiple studies | Individuals with SMI generally had lower screening rates, with 20% to 30% lower receipt of screenings for breast, cervical, and colorectal cancers | The majority of evidence demonstrates poorer quality of preventive services for individuals with SMI compared with the general population |
| Breast, colon/Druss 201057   | M     | RCT         | Trial comparing medical care management for individuals with SMI vs usual care | N = 407 patients in CMHC in Atlanta, Georgia | At 12-mo follow-up, the intervention group received an average of 58.7% of recommended preventive services compared with 21.8% in the usual care group (P < .001) | Care management was associated with significant improvement in primary care process and outcome measures |
| Cervical/Weitlauf 201358     | D     | PTSD O      | Study comparing receipt of recommended cervical cancer screening in 3 diagnostic groups: 1) PTSD, 2) depression, and 3) no psychiatric diagnosis | N = 34,213 women from the national VA database | Overall, 77% of women with PTSD, vs 75% of those with depression and 75% of those without psychiatric illness, received cervical cancer screening during the study observation period (P < .001) | VA health care environment may “level the playing field” for those with psychiatric illness |
| Cervical/Abrams 201229       | M     | CC          | Case-control study comparing rates of cervical cancer screening and acute care visits among women with and without a diagnosis of mental illness | N = 105,681 female Maryland Medicaid enrollees | There was increased cervical cancer screening in women with psychosis (OR, 1.46), bipolar disorder/mania (OR, 1.39), and depression (OR, 1.78) and decreased OR for women with substance use (OR, 0.8) | People within the Maryland Medicaid system with mental illness appear to be able to access preventive care; more outreach is needed for women with substance use |
| Multiple/Barley 201360       | M     | SR          | Systematic review of the effectiveness of interventions to encourage cancer screening in adults with SMI | Multiple          | There is no evidence for any method of increasing cancer screening specifically for people with mental illness | Evidence-based approaches to increasing cancer screening in individuals with SMI are greatly needed |
| Multiple/ Irwin 201461       | S     | Review      | Review of health disparities in cancer care among patients with schizophrenia | Multiple          | Patients with schizophrenia are less likely to have up-to-date cancer screenings | Patient-level, provider-level, and systems-level factors contribute to low rates of cancer screening; psychiatrists can facilitate screening |
| CANCER TYPE/ PRIMARY AUTHOR | MH DX | STUDY DESIGN | DATA COLLECTION/METHODS | SAMPLE AND SETTING | RESULTS/DATA | CONCLUSIONS |
|-----------------------------|-------|--------------|-------------------------|-------------------|-------------|-------------|
| Breast/Rahman 2014⁶²         | M     | Review       | Review article on pathophysiology, clinical implications, and pertinent pre-clinical data regarding the use of antipsychotics in patients with breast cancer | Multiple studies | Prolactin promotes breast cancer cell growth regardless of receptor status, and breast cancer patients with elevated prolactin levels have quicker disease progression and lower survival rates; most first-generation antipsychotics significantly elevate serum prolactin levels | A decision to discontinue or change medications requires consideration of the risks and benefits given the patient's mental illness type and severity, cancer staging, and patient and family preferences |
| Breast/Sharma 2010⁶³         | S     | O            | Cohort study of breast cancer treatment in women with schizophrenia from 1993 to 2009 | N = 90,676 patients from UK NHS records | Thirty women (81%) presented with early breast cancer, and 7 (19%) presented with metastatic disease; treatment outcomes, trial involvement, compliance, and ability to provide informed consent were similar to previously published cohort data | Schizophrenia does not affect treatment delivery or outcomes in women with breast cancer; the presence of schizophrenia should not be a limiting factor for entry into clinical trials |
| Colon/Baillargeon 2011⁶⁴    | M     | O            | Retrospective review of SEER-Medicare-linked data on all individuals diagnosed with colon cancer between January 1, 1993, and December 31, 2005 | N = 8670 participants aged 67 y and older with a diagnosis of colon cancer in the SEER-Medicare database | Participants with mental illnesses were more likely to have been diagnosed with colon cancer at autopsy (4.4% vs 1.1%; P < .001) and with an unknown stage of cancer (14.6% vs 6.2%; P < .001); to have received no surgery, chemotherapy, or radiation therapy (ARR, 2.09; 95% CI, 1.86–2.35); and to have received no chemotherapy for stage III cancer (ARR, 1.63; 95% CI, 1.49–1.79) | Public health initiatives are needed to improve colon cancer detection and treatment in older adults with mental disorders |
| Lung/Bergamo 2014⁶⁵          | S     | O            | Retrospective review of SEER-Medicare-linked data from patients aged 66 y or older with confirmed, primary NSCLC diagnosed between 1992 and 2007 | N = 96,702 patients with NSCLC in SEER-Medicare database | Patients with schizophrenia were less likely to present with late-stage disease, undergo appropriate evaluation, or receive stage-appropriate treatment (OR, 0.82; 95% CI, 0.73–0.93; P < .050 for all comparisons; OR, 0.50; 95% CI, 0.43–0.58); survival was decreased among patients with schizophrenia, although not after controlling for treatment received | Elderly patients with schizophrenia present with earlier stages of lung cancer but are less likely to undergo diagnostic evaluation or to receive stage-appropriate treatment, resulting in poorer outcomes |
### TABLE 3. Continued

| CANCER TYPE/ PRIMARY AUTHOR | MH DX | STUDY DESIGN | DATA COLLECTION/METHODS | SAMPLE AND SETTING | RESULTS/DATA | CONCLUSIONS |
|-----------------------------|-------|--------------|-------------------------|--------------------|--------------|-------------|
| Multiple/Foti 2005 | M | O | Study of treatment preferences in response to hypothetical medical illness scenarios | N = 150 community-residing adults with SMI in Massachusetts | For the scenario involving pain medication for incurable cancer, most participants chose aggressive pain management, even if cognition might be affected; few participants thought a doctor should provide patients with enough medication to end their life; for the scenario of irreversible coma, respondents were divided in their choice regarding life support | Persons with SMI were able to designate treatment preferences in response to EOL health state scenarios; although most participants had not previously participated in advance care planning, they were interested in the topic and participated |
| Multiple/Howard 2010 | M | Review | Review of multiple articles looking at SMI and cancer incidence and risk factors, screening, and equity of access to treatment and care | Multiple studies | Patients with SMI are less likely to receive cancer screenings; there is insufficient evidence to determine whether unique barriers exist for individuals with SMI; for treatment, patients with SMI have poorer access to diagnostic and treatment services for health complaints and have delays in help seeking; are less likely to receive surgery for esophageal cancer; have more treatment complications; and have higher case-fatality rates for multiple cancers | Severe mental illness is associated with behaviors that predispose an individual to an increased risk of some cancers, disparities in screening for cancer, and higher case-fatality rates; inequalities in care need to be addressed by all healthcare professionals involved, including those from mental health services and the surgical and oncology teams |
| Multiple/Damjanovic 2006 | S | Review | Review of behaviors that increase the risk of cancer in patients with schizophrenia | Multiple studies | Some antipsychotics increase prolactin, which may increase breast and endometrial cancer risk; studies of overall malignancy risk have conflicting results; some psychotropic drugs can inhibit chemotherapy metabolism | Treatment of cancer in individuals with schizophrenia should include evaluation of risk factors, drug interactions, risk-benefit analysis of treatment options, and efforts to promote treatment adherence |
| Multiple/Damjanovic 2006 | S | Review | Review summarizes known disparities in cancer prevention, diagnosis, treatment, and EOL care among individuals with schizophrenia | Multiple studies | Patients with schizophrenia have delays in diagnosis and treatment, perhaps due to stigma; are less likely to have esophageal or colorectal cancer surgery; have higher postsurgery mortality and postoperative complication rates; and are less likely to participate in clinical trials | Provides should assume decisional capacity and address suicidality, violence, and homelessness |

**AOR** indicates adjusted odds ratio; **ARR**, adjusted relative risk; **ART**, adjuvant radiation therapy; **BMI**, body mass index; **CC**, case-control; **CI**, confidence interval; **CMHCs**, Community Mental Health Centers; **D**, depression; **DX**, diagnosis; **EOL**, end of life; **M**, multiple mental illnesses; **MA**, meta-analysis; **MH**, mental health; **NAEs**, neuropsychiatric adverse events; **NSCLC**, nonsmall cell lung cancer; **O**, observational; **OR**, odds ratio; **PTSD**, post-traumatic stress disorder; **RCTs**, randomized controlled trials; **RR**, relative risk; **S**, schizophrenia; **SEER**, Surveillance, Epidemiology, and End Results Program; **SMI**, serious mental illness; **SR**, systematic review; **SRMA**, systematic review and meta-analysis; **UK NHS**, United Kingdom National Health Service; **VA**, Veterans Affairs.

*A more complete version of Table 3 is provided in Supporting Information Tables 1 through 3 (see online supporting information).*
adults with schizophrenia newly exposed to antipsychotic drugs who show a pattern of rapid weight gain and/or glucose dysregulation. Other pharmacological agents have been considered for use in weight management in patients taking antipsychotic drugs, including amantadine, reboxetine, sibutramine, and topiramate. However, there is less data for these agents, and all can have significant side effects (such as gastrointestinal side effects), especially for people with mental illness who are taking other medications.

Medication-associated weight gain is also a common clinical concern in patients with depression. Contributing factors include increased use of antipsychotic medication in treatment-resistant depression and ongoing questions regarding the effects of selective serotonin reuptake inhibitors on weight. In the most comprehensive study to date, Blumenthal et al reported that, compared with citalopram (and other selective serotonin reuptake inhibitors), individuals who were treated with bupropion, amitriptyline, and nortriptyline had a significantly decreased rate of weight gain. However, the mean ± standard deviation (SD) 12-month weight gain associated with citalopram was quite modest at 1.2 ± 5.3 kg, and 16% of patients had weight gain greater than 7%.

A recent qualitative study explored the contexts and barriers to health in people with SMI and remarked on “unhealthy local environments,” including lack of available healthy food and safe places to exercise as well as the preponderance of fast food. Notably, very few interventions were identified that addressed the “obesogenic environment” in which many people with mental illness live or the challenges they face given their limited financial resources. A novel pilot RCT by Jean-Baptiste et al is a notable exception: In addition to a 16-week behavioral modification and physical activity curriculum, participants in the intervention group were provided with a specific listing of healthy foods they could purchase, for which they would be reimbursed up to $25 a week. The weekly reimbursement reinforced health food purchasing and at the same time served as a financial incentive for attendance. Participants in this pilot showed nonclinically significant weight loss but, remarkably, weight loss continued 6 months after the intervention. However, even this study was an individually focused intervention and did not address higher level issues in the “obesogenic environment.” In summary, the current data regarding weight management for people with mental illness are limited, with promising interventions by Daumit et al and Wu et al. Additional intervention studies are underway, such as that by Cabassa et al, examining the use of a peer-led group lifestyle-modification program with supportive housing agencies that provide both housing and individualized support services to people with SMI.

Tobacco-Related Interventions
Although multiple studies indicate that people with SMI want to quit smoking, effective treatment is underused, and there is a lack of population-specific smoking-cessation programs. People with SMI may require specialized smoking-cessation programs because of the complex interplay of social, psychiatric, and genetic factors that contribute to their high smoking rates. As in the general population, smoking-cessation efforts for people with mental illness include some combination of behavior modification, nicotine replacement therapy (NRT), and pharmacological therapy (bupropion or varenicline).

The data on the use of NRT alone are limited by heterogeneity of trials and short follow-up periods. A potentially promising approach in this population is treatment with off-label, high-dose NRT (greater than one 21-mg patch). One small study compared high-dose NRT (42 mg) versus regular-dose NRT (21 mg) in people with schizophrenia and found that high-dose NRT was well tolerated, although the study failed to find a significant difference in abstinence rates between the 2 groups. A single-arm study by Selby et al in patients with psychiatric comorbidities using escalating doses of NRT found a significant reduction in cigarettes per day (mean ± SD decrease, 18.4 ± 11.5 cigarettes per day), as confirmed by expired carbon monoxide levels (mean ± SD decrease, 13.5 ± 13.0 ppm), with no significant changes in plasma nicotine concentrations during the course of NRT dose titration. In that study, the mean ± SD NRT dose was 32.7 ± 16.4 mg/day (range, 7–56 mg/day).

The use of bupropion and varenicline in this population has been limited by theoretical and reported concerns of adverse neuropsychiatric events, including suicide, and initial safety studies did not include people with mental illness. The US Federal Drug Administration has required a black-box warning regarding the risk of serious adverse psychiatric events for both bupropion and varenicline. Two Cochrane reviews recently examined studies involving pharmacological smoking-cessation interventions among people with schizophrenia and depression. The review by Tsoi and colleagues confirmed the importance of pharmacological therapy with bupropion to achieve tobacco cessation for people with schizophrenia. However, van der Meer et al produced a report with mixed findings, and they concluded that the use of bupropion may increase long-term cessation in smokers with past depression; but, paradoxically, there was no evidence to support the use of bupropion in smokers with current depression. All trials with bupropion monitored participants’ mental health during treatment, and none reported adverse effects.

With respect to varenicline, Gibbons and Mann reviewed data from RCTs and from a large Department of Defense observational study to assess its efficacy. Their review of the
evidence offered significant support for the superior efficacy of varenicline relative to both placebo and bupropion in individuals with and without a recent history of a psychiatric disorder. With respect to safety, their review revealed no indication that varenicline is associated with adverse neuropsychiatric events\(^{50}\); and, in a corresponding editorial, Evins stated that “varenicline doubles to triples the likelihood of quitting smoking over placebo, and its most common side effects are nausea and vivid dreams. . . it is time to unring the alarm bell on varenicline and use this effective medication on a larger scale.”\(^{73}\)

In contrast, another study assessed neuropsychiatric adverse events associated with varenicline and, using a method for estimating the probability of adverse drug reactions, concluded that varenicline was responsible for probable causality in 76% of cases and definite causality in 12% of cases.\(^{69}\) Although that study was limited to 25 reports of adverse events, the possibility of adverse psychiatric events with varenicline could not be ruled out. Pfizer is currently completing a phase 4, randomized, double-blind, active and placebo-controlled, multicenter study evaluating the neuropsychiatric safety and efficacy of 12 weeks of varenicline tartrate 1 mg twice daily and bupropion hydrochloride 150 mg twice daily for smoking cessation in patients with and without a recent history of psychiatric disorders. Results are expected to be released in the third quarter of 2015. This will provide very helpful further guidance for clinicians.\(^{74}\)

In terms of treatment complications among people with mental illness, clinicians need to be aware of potential changes in metabolism of certain psychotropic medications with reduced smoking. Smoking substantially lowers blood levels of numerous antipsychotics (eg, haloperidol, fluphenazine, chlorpromazine, thioridazine), as well as multiple other medications, by increasing cytochrome P450 metabolism. People who successfully cut down or quit potentially need significantly lower doses of these medications.\(^{152}\) Importantly, tobacco cessation in people with SMI needs to address the organizational environment of mental health agencies that use cigarettes as incentives and have high levels of staff tobacco use. One promising model is the “Addressing Tobacco Use Through Organizational Change” or ATTOC model currently being tested by Dr. Ziedonis and colleagues at the University of Massachusetts.\(^{153}\)

**Obesity and Tobacco Recommendations**

The following section outlines multilevel recommendations for addressing obesity and tobacco use in people with mental illness:

**Individual level**

- Strongly consider metformin therapy for weight loss in 3 high-risk groups\(^{53}\):
  - Obese people who have schizophrenia with evidence of glucose dysregulation, irrespective of antipsychotic drug treatment;
  - Obese people who have schizophrenia without current evidence of glucose dysregulation but with a strong family history of diabetes; and
  - Young adults with schizophrenia who are newly exposed to antipsychotic drugs and have a pattern of rapid weight gain and/or glucose dysregulation.

- Actively address tobacco dependence in all people with mental illness, and consider bupropion and varenicline in psychiatrically stable patients.
- Monitor need for decreased doses of medications in people who decrease smoking.
- Consider the promotion of healthy lifestyle and physical activity interventions in all people with mental illness.\(^{51,52}\)

**Organizational level**

- Increase efforts to reduce obesogenic environments in agencies that serve people with mental illness, such as increasing structured opportunities for physical activity and providing healthier meals and snacks.
- Eliminate the use of tobacco and unhealthy food as incentives in mental health treatment agencies.
- Support smoke-free environments in mental health treatment agencies.
- Deliver health interventions in community settings that regularly serve people with SMI to address access barriers.
- Include healthy lifestyle goals in treatment planning for people with mental illness.

**Community level**

- Increase efforts to reduce obesogenic environments in low-income neighborhoods, where people with SMI are more likely to reside, by partnering with community agencies to advocate for farmer’s markets, supermarkets, and access to safe spaces for physical activity.

**Policy level**

- Increase funding for high-quality, multilevel intervention trials addressing obesity and tobacco use in people with mental illness.
- Provide insurance reimbursement for the screening, management, and treatment of obesity and tobacco-cessation programs as part of mental health treatments.

**Screening**

Studies generally show lower rates of cancer screening in people with schizophrenia or psychosis\(^{59,109,112,118,119}\) even in systems that provide free access to screening services. However, these studies are all either retrospective cross-sectional or case-control studies. The majority focus
on breast and cervical cancer screening, with a few considering colorectal cancer screening. The available data for women with depression are mixed, with essentially equal numbers of studies showing decreased rates or no differences in breast and cervical cancer screening and conflicting results for rates of colon cancer screening. Several studies note that women with depression access the health care system more frequently; therefore, in some settings, they may be offered more opportunities for preventive services. The finding by Weitlauf et al of equal rates of cervical cancer screening in women veterans with depression and women veterans without a psychiatric diagnosis suggests that the Veterans Administration health care environment may “level the playing field” for those with psychiatric illness. Despite this conflicting evidence, a systematic literature review of cancer screening in women concluded that “lower cancer screening utilization persists across the spectrum of mental illness diagnosis and severity,” and noted that studies finding no differences were often limited by small, or less representative, samples.

Notwithstanding the documented disparities, few interventions exist to increase screening rates for persons with SMI; and, disappointingly, a recent Cochrane review found “no RCT evidence for any method of encouraging cancer screening uptake in people with SMI.” However, one RCT not mentioned in the Barley review was the Primary Care Access, Referral, and Evaluation (PCARE) study by Druss et al, in which nurse care managers followed a manualized or standardized, semistructured protocol to improve the use of preventive and primary care services in people with SMI. At 12-month follow-up, the intervention group received an average of 58.7% of recommended preventive services compared with 21.8% in the usual care group \( (P < .001) \). Although cancer prevention and screening services were not reported individually, mammography and sigmoid screening were included as measures of preventive care.

In addition, two of the authors (L.C.W. and K.H.) recently developed a shared decision-making and navigation intervention to increase breast cancer screening uptake in women with SMI. A 6-month pilot study of this intervention with 22 formerly homeless women with SMI who were not up to date on mammography screening was recently completed. Sixty-six percent of women completing the study reported receiving a mammogram, and there was a significant decrease in decisional conflict immediately postintervention, which was maintained at the 6-month follow-up.

Screening Recommendations

The following section outlines multilevel recommendations to promote cancer screening in people with mental illness:

**Individual level**
- Provide sensitive cancer screening environments for people with mental health issues that allow for limited wait times and orientation to equipment and procedures.

**Interpersonal level**
- Consider using and adapting shared decision-making tools for people with mental illness to increase engagement in prevention activities.
- Provide a community health worker or peer counselor to provide health education and help the patient navigate the screening process.

**System level**
- Increase awareness of cancer screening disparities among mental health service providers.
- Increase integration of primary and behavioral health services with an emphasis on screening and prevention.
- Decrease the complexity of obtaining screening services.
- Promote programs to educate peer counselors (specially trained lay people with personal experience of mental illness) in prevention and wellness to deliver services.

**Policy level**
- Advocate for enhanced reimbursement for interdisciplinary care coordination and preventive care services in people with complex medical and psychiatric morbidities.

**Treatment**

The majority of cancer treatment studies in individuals with SMI have focused on patients with cancer and schizophrenia or major depression, and several have examined cancer treatment across multiple psychiatric conditions. To date, this research has been observational and cross-sectional. These studies reveal numerous disparities for patients with SMI and cancer in diagnosis and time to treatment; receipt of chemotherapy, radiation, and surgery; and clinical trial participation. Evidence of disparities is particularly strong for individuals who have schizophrenia and other conditions that include psychosis.

One important barrier to achieving optimal cancer outcomes is delayed diagnosis. A study of Surveillance, Epidemiology and End Results-Medicare-linked data showed that individuals with mental illness (defined as mood disorders, psychotic disorders, dementia, substance abuse and dependence disorders, and other) and colon cancer are more likely to have unstaged colon cancer or a diagnosis of colon cancer at autopsy. Another Surveillance, Epidemiology and End Results-Medicare analysis revealed that patients with schizophrenia and nonsmall cell lung cancer are less likely to have appropriate evaluation. A study of Swedish adults with schizophrenia who died of cancer showed that those individuals were less likely to have a
cancer diagnosis before death.\(^{37}\) One examination of women with major depression or anxiety in 6 Boston-area health centers found no association between these diagnoses and the time to resolution of abnormal mammogram or Papanicolaou test results.\(^{125}\)

In general, patients with SMI, particularly schizophrenia, are less likely to receive appropriate chemotherapy, radiation therapy, or surgery. A study in Western Australia, with a data set consisting of over 100,000 new cancer cases, found that individuals with mental illness received fewer sessions of chemotherapy in general and were less likely to receive surgery overall as well as radiation therapy for certain cancer sites.\(^{38}\) Other studies similarly found that patients with a major mental illness are less likely to receive chemotherapy, radiation, or surgery for colon cancer\(^{64}\) and are less likely to have surgery for oral cancer.\(^{130}\) Individuals with schizophrenia are less likely to receive stage-appropriate treatment for lung cancer,\(^{127}\) surgery for esophageal cancer,\(^{61}\) and referrals to clinical trials.\(^{61}\) There are a few exceptions to this pattern of treatment disparities, most notably for chemotherapy rates among breast cancer patients with schizophrenia.\(^{61,63,124}\)

Those with SMI are more likely to have treatment complications and poorer outcomes. Women with psychiatric diagnoses undergoing mastectomy are more likely to have complications and longer hospitalizations.\(^{123}\) A study of women with stage 0 through II breast cancer found that those with a history of major depressive disorder had greater declines in physical functioning than those with no history of depression.\(^{122}\) Patients with schizophrenia have a higher rate of postoperative complications and postsurgery mortality.\(^{61}\) Finally, as previously noted, many studies have found that individuals with SMI have disproportionately higher cancer mortality rates.\(^{37,44,61,64,65,130}\)

Patient-level, provider-level, and systems-level factors all contribute to these disparities in diagnosis, treatment, and outcomes. Patient-level factors include delays in help-seeking because of mental health symptoms, such as the disorganized thoughts, paranoia, and decreased pain sensitivity associated with schizophrenia.\(^{61}\) Increased prevalence of health risk behaviors and comorbidities, such as chronic obstructive pulmonary disease, obesity, diabetes, and cardiovascular disease, can complicate treatment and contribute to poorer outcomes.\(^{38,44,122}\) Fragmented primary, oncology, and mental health services\(^ {129}\); providers’ stigmatizing beliefs or behaviors\(^ {128}\); and “diagnostic overshadowing”—when clinicians misattribute physical symptoms to a mental illness rather than, correctly, to a physical illness—may also delay appropriate diagnosis and treatment, especially for individuals with schizophrenia and other SMI.\(^ {44,61}\)

Once diagnosed, patients often face perceptions that they are “difficult patients” who lack the capacity to make treatment decisions or adhere to treatment regimens or may become violent.\(^ {44,61,124}\) Barriers to clinical trial enrollment include patients’ mistrust of research, lack of communication to patients about relevant trials, and concerns about patients’ ability to provide informed consent, which has resulted in outright exclusion of people with SMI in many of these studies.\(^ {61}\) Finally, individuals with SMI are more likely to experience social isolation,\(^ {156}\) poverty,\(^ {64}\) and homelessness,\(^ {155}\) all of which present numerous challenges to providing treatment and end-of-life care.\(^ {51}\)

**Treatment Recommendations**

The following section outlines multilevel recommendations for improving cancer treatment in people with mental illness:

**Individual level**

- Patients with SMI may benefit from a brief hospitalization after their first chemotherapy treatment or a longer postoperative stay.\(^ {61}\)
- Radiation therapy, in which the patient is alone in the treatment room receiving instructions from an outside voice, can be distressing for patients with severe anxiety, paranoia, or auditory hallucinations. A pretreatment visit to the radiation therapy suite with explanations of the equipment and procedure may reduce patients’ anxiety or help the patient and care team decide that radiotherapy is not appropriate.\(^ {44}\)

**Interpersonal/provider level**

- Consciously avoid the tendency toward “diagnostic overshadowing,” or attributing physical symptoms that may indicate cancer to the patient’s mental illness. Potential organizational-level solutions to avoid diagnostic overshadowing include having peer navigators help in the coordination of care, better integration of care between mental health and health providers, and health care manager programs.\(^ {128,154}\)
- Improve information sharing strategies between medical and mental health providers via shared electronic health records, health information exchanges, or personal health records.
- Assess decisional capacity on an individual basis, and tailor communication based on cognitive deficits or other psychiatric symptoms.\(^ {44,124}\)
- Be aware of the many drug-drug interactions between psychiatric medications and chemotherapeutic drugs. For example, clomipramine, diphenhydramine, duloxetine, haloperidol, paroxetine, sertraline, and fluoxetine inhibit chemotherapy metabolism of some chemotherapeutic agents, while carbamazepine, oxcarbazepine, and St. John’s Wort increase chemotherapy metabolism.\(^ {43,44}\)
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