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# Influence of Depression on Treatment and Survival: A Population-based Study in Patients with Breast Cancer in Kentucky

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# Influence of Depression on Treatment and Survival:

# A Population-based Study in Patients with Breast Cancer in Kentucky

# Contents

## *NOTES*

### Breast Cancer and Depression among Breast Cancer Survivors

Breast cancer starts when cells in the breast begin to grow out of control. These cells usually form a tumor that can often be seen on an x-ray or felt as a lump. The tumor is malignant (cancer) if the cells can grow into (invade) surrounding tissues or spread (metastasize) to distant areas of the body. Risk factors for developing breast cancer include being female, obesity, lack of physical exercise, drinking alcohol, hormone replacement therapy during menopause, ionizing radiation, early age at first menstruation, having children late or not at all, older age, prior history of breast cancer, and family history[1]. Except for skin cancer, breast cancer is the most commonly diagnosed cancer and the second leading cause of cancer mortality in women. Currently, more than three million women are living with breast cancer in the United States[2]. Previous studies have illustrated breast cancer survival is determined by factors including age, ethnicity, comorbidity, socio-economic factors, stage of cancer at diagnosis, and treatment[3-7].

Depression (major depressive disorder or clinical depression) is a common but serious mood disorder. It causes severe symptoms that affect how you feel, think, and handle daily activities, such as sleeping, eating, or working. To be diagnosed with depression, the symptoms must be present for at least two weeks[8]. In fact, cancer and treatment-related symptoms can be major stressors in a patient with breast cancer who is undergoing treatment for the disease. Therefore, addressing the impact of breast cancer and its treatment on long-term outcomes is an important issue. Depression is a noticeably common mental health outcome among breast cancer survivors, and its hypothesized association with adverse survival in breast cancer patients has been of interest in the past decade. Studies estimated that about 10% to 25% of breast cancer patients experience depression, which is higher compared with matched control group[9,10];

**Previous Studies about Depression on Survival and Treatment Among Breast Cancer Patients**

1. Survival after Early-stage breast cancer of women previously treated for depression: A nationwide Danish cohort study.

- Year:2017
- Journal: Journal of Clinical Oncology
- Sample Populaiton:45325 women with early breast cancer in Denmark from 1998 to 2011(744 women had a previous hospital contact, 6068 treated with antidepressants.
- Conclusion: Women previously treated for depression constitute a large subgroup of patients with breast cancer who are at risk for receiving nonguideline breast cancer treatment. Which probably contributes to poorer overall and breast cancer-specific survival.
- Depression Identification:1. To capture the most severe) # hospital months before diagnosis of cancer (ICD-8) ;2. Treatment with depressants form 3 months before diagnosis of breast cancer and 3 years previously (Prescription Registry).
- Results: 1.  Those with previous hospital contact for depression or who dad used antidepressants were likely to be older, have less education, live alone, have comorbid somatic disease, and have breast cancer in later canlerder year. 2.  More women who had antidepressants received only a biopsy and not surgery and were therefore more likely to have unknown tumor size, number of tumor -positive lymph nodes, and ER status.  3.Statistically significantly fewer women who had used antidepressants were allocated to guideline systemic adjuvant therapy.
  4. 80% previously treated for depression still use antidepressants after cancer diagnosis. 23% who not, started to use after diagnosis of breast cancer.
  5. Women who had used antidepressants were not allocated to guideline breast cancer treatment (p<0.05, OR=1.14).   Previously hospital contact (OR=1.32, 95%CI (0.99,1.77)).
  6.There's no difference in term of survival among patients with and without depression, if they all received adjuvant treatment according to the guidelines.
- Limitaion:1. Other conditions such as anxiety and pain might account for more than 25 % of prescribed antidepressants.   2. Possible misclassification of breast cancer specific death.

2. <u>The association of mood disorders with breast cancer survival: an investigation of linked cancer registration and hospital admission data for South East England.</u>

- Year: 2016
- Journal: Psychology
- Sample Population: 77173 patients diagnosed with breast cancer in South East England from 2000 to 2009(depression = 955). Of these patients, 422 had a prior record of a diagnosis of depression, and 533 had a new record of depression after the cancer diagnosis.
- Conclusion: There is evidence that English breast cancer patients with depression and bipolar recorded in routine hospital data have worse overall survival than those without these mood disorders.
- Depression Identification: Patients with a diagnosis of At least one depressive episode (ICD‐10 F32) and recurrent depressive disorder (ICD‐10 F33) where these were recorded within HES in the 3 years before and the year following the cancer diagnosis. Patients with a diagnosis of either a recurrent depressive disorder or a depressive episode were grouped together as 'depression', either a recurrent depressive disorder or a depressive episode were grouped together as 'depression'.
- Results: 1. A record of depression was a predictor of worse overall survival in breast cancer patients (adjusted HR = 1.33, 95% CI: 1.20–1.48, $p < 0.001$), while the effect of bipolar was not statistically significant (adjusted HR = 1.33, 95% CI: 0.97–1.82, $p = 0.079$). New recordings of depression and bipolar diagnoses following a cancer diagnosis appeared better predictors of overall survival than a prior history of either. 2. patients with a record of depression before or following the breast cancer diagnosis had a higher risk of dying even after adjusting for age, ethnicity, deprivation, comorbidities, stage of disease and treatment (fully adjusted HR = 1.33, 95% confidence interval (CI): 1.20–1.48, $p < 0.001$). The timing of the onset of depression appeared to be important. Depression recorded prior to the cancer diagnosis had a high unadjusted hazard ratio of 2.29 (95% CI: 1.98–2.64, $p < 0.001$) (Table 2), but this reduced to 1.23 (95% CI: 1.07–1.42, $p = 0.005$) after adjustment, with the main attenuating factors being age, comorbidity and stage. Depression after the cancer diagnosis, when no previous history of depression had been recorded, demonstrated a high hazard ratio of 1.69 (95% CI: 1.46–1.95, $p < 0.001$) but was less affected by adjustment (HR = 1.45, 95% CI: 1.25–1.68, $p < 0.001$).
- Limitation: 1. There were several tumor factors that were not available to include in the study, including estrogen receptor, progesterone receptor and HER‐2 status; performance status; or more detailed staging information.

3. Prospective association of depression with survival: a population-based cohort study in patients with newly diagnosed breast cancer

- Year: 2014
- Journal: Breast Cancer Research Treatment
- Sample Population: 1646 eligible patients with invasive female breast cancer stages I-IV from 2004 to 2009(562 presented with depression symptoms, 260 of these patients met clinical levels of depression.
- Conclusion: Depression is strongly associated with mortality in younger patients with early stage breast cancer.
- Depression Identification: Patients were routinely assessed for emotional distress after cancer diagnosis but before treatment initiation. (Base on DSM-IV-TR criteria)
- Results: 1. (Stage I-III) Depression on all-cause mortality (HR=1.54. p=0.024), and breast cancer-specific mortality (HR=1.51, p=0.084). Age did not moderate association between depression and mortality. 2. Depression has an impact on all-cause and cancer-specific mortality in patients with stage I and Stage II(HR=2-2.5).
  3.  Age moderates the association between depression and all-cause mortality in patients with stage I breast cancer. Younger patients at the age of 45(HR=9.82) with a depression compared to non-depresses patients (HR=9.82, p= 0.002).   Mean age of 57 (HR=3.69, p=0.007). 4. Analyses by tumor stage revealed that the effect of depression on mortality is mostly driven by patients with earlier stage breast cancer (stage I and Stage II).
- Limitation: 1. The relative brief depression measure does not substitute for a diagnosis of depression based on a structured clinical interview.

4. Poor physical factors predict time to additional breast cancer events and mortality in breast cancer survivors

- Year: 2011
- Journal: Psychology
- Sample Population "Women with early stage breast cancer (n=2967) at 7 study sites between 1995 and 2000. Breast cancer diagnosis within the past 4 years of primary

operable invasive stage I ($\geqslant$ 1 cm), II, or IIIA breast carcinoma; age 18 – 70 years at time of diagnosis;

- Conclusion "Social support, optimism, hostility, and depression prior to randomization into a dietary trial were assessed. However, Except for hostility, none of the other psycho-social variables predicted either outcome.

- Depression Identification: "Depression was assessed by the 8-item Center for Epidemiologic Studies Depression screen ( $\alpha$ =0.73). A value $\geqslant$ 0.06 in the logarithmic scale suggests clinical levels of depressive symptoms and the possibility of diagnosable mood disorder.

- Results: "Social support, optimism, hostility, and depression prior to randomization into a dietary trial were assessed. However, except for hostility, none of the other psycho-social variables predicted either outcome."

5.   Psychosocial factors and survival of young women with breast cancer: a population-based prospective cohort study

- Year: 2008
- Journal: Journal of Clinical Oncology
- Sample Population: A population-based sample of 708 Australian women diagnosed before age 60 years with nonmetastatic breast cancer was observed for a median of 8.2 years. 73(3%) of these patients (HADs)were defined as with depression.
- Conclusion: There were no statistically significant associations between any of the measured psychosocial factors and distant disease-free survival or overall survival from the adjusted analyses. The findings do not support the measured psychosocial factors being an important influence on breast cancer outcomes.
- Depression Identification: Depression and anxiety, coping style, and social support were assessed at a median of 11 months after diagnosis using a face-to-face interview-participants were administered epidemiologic questionnaires.
- Results: 1. Greater anxious preoccupation was associated with younger age at diagnosis (P = .03), higher tumor grade (P = .02), and greater number of involved axillary nodes (P = .008).   2.Because the prevalence of probable depression (HADS score of > 10) was low (3%), analysis was repeated by, dichotomizing the HADS score at a cut point of 8 (possible or probable depression v depression unlikely), and the results did not change substantially (data not shown).

6. <u>Effect of depression on diagnosis, treatment, and survival of older women with breast cancer</u>

- Year: 2004
- Journal: Journal of American Geriatric Society
- Sample Population: Women aged 67 to 90 diagnosed with breast cancer between 1993 and 1996 included in the SEER Medicare linked database. (N=24696, 7.5% with prior depression).
- Conclusion: Women with a recent diagnosis of depression are at greater risk for receiving nondefinitive treatment and experience worse survival after a diagnosis of breast cancer, but difference in treatment do not explain the worse survival.
- Depression Identification :2 years before breast cancer diagnosis (identified by ICD-9-CM code).
- Results: 1. The women with a prior diagnosis of depression were on average older, more likely to be non-Hispanic white, less likely to be married, likely to have more comorbid illnesses. 2. There were no differences in tumor size at diagnosis in women with or without a prior diagnosis of depression. After controlling doctor visits, a diagnosis of depression was associated with increased size.
  3. Women with a history of depression were significant less likely to receive standard cancer treatment. 4 Receipt of definitive treatment did not appear to mediate this increased risk of death associated with depression.
- Limitation: Only included women with breast cancer diagnosed at the age of 67 years or older, limiting the generalizability of result.

7. <u>Health-Related Quality of Life and Psychosocial Status in Breast Cancer Prognosis: Analysis of Multiple Variables</u>

- Year: 2004
- Journal: Journal of Clinical Oncology
- Sample Population: 397 women diagnosed with breast cancer at participating University of Toronto teaching hospitals between1991 and 1996 (younger than 75, with T1 to T3, N0/N1, M0 breast cancer.
- Conclusion: health-related quality of life (HRQOL) and psychosocial status at diagnosis and 1 year later are not associated with medical outcome in women with early-stage BC.

- Depression Identification: Based on self-report questionaire to identify distress status.
- Results: Little convincing evidence was found that HRQOL or the psychosocial variables studied have important associations with distant disease-free survival (DDFS) or overall survival (OS) in women with newly diagnosed locoregional breast cancer.
- Limitation: 1. measure of mood (POMS) provides scores for depression and anxiety, these scores are not intended to be measures of clinical depression or anxiety.
  2. Physiologic, compliance-related mechanisms, or social support in this research.

# Initial Analysis Plan

Outline:

- Purpose
    1. To determine whether getting depression is associated with urban-rural/Appalachia-non-Appalachia status among breast cancer survivors;
    2. To determine whether diagnosed with depression is associated with breast cancer treatment;
    3. To examine the association between depression treatment and urban-rural/Appalachia-non-Appalachia status among breast cancer survivors diagnosed with depression;
    4. To find whether depression predicts worse survival among breast cancer survivors.
- Data source: The Kentucky Cancer Registry (KCR) linked data, American Community Survey (ACS) census tract file.
- Study population
- Key variables
    1. Depression Status (yes or no)
    2. Treatment of depression
    3. Cancer survival
    4. Cancer treatment
    5. Rural/urban status
    6. Appalachia-Non-Appalachia status
- Other independent variables
- Statistical analysis: Chi-square; Logistic Regression; Cox Regression Model

# Selection Criterion

- Cancer cases: First Primary female breast cancer survivors age >=20, diagnosed at 2007-2011;
- Claims Data: Linked medicare, Medicaid, and private insurance claims data, 2006-2013;
- Continuous enrollment: Not required yet. Indicator variable which indicates enrollment is needed, including 12 months prior, 12 months after.
- Claims to define depression: 13 months (Month at the cancer diagnosis and 12 months after the diagnosis).
- The current plan is to include all patients who had depression after cancer diagnosis from claims; for these without depression, only include patients who had continuous coverage.

***Variables and definitions***

Depression status (Yes or no Identified by ICD-9-CM code):

. Major depressive disorder, single episode:296.20, 296.21,296.22,296.23,296.24, 296.25,296.26;
. Major depressive disorder, recurrent episode:296.30, 296.31, 296.32,296.33,296.34, 296.35, 296.36;
. Depressive type psychosis: 298.0;
. Neurotic depression: 300.4;
. Adjustment disorder with depressed mood: 309.0;
. Prolonged depressive reaction: 309.1;
. Depressive disorders, not classified: 311.0.

Depression status will be calculated for both prior cancer diagnosis and after cancer diagnosis. Psychotherapy (Based on the following code to identify whether patients received Psychotherapy or not).

❖ Revenue center codes: This only works for Medicare data (output file only)

0114(Private medical or general-psychiatric)

0124(Semi-private 2 bed (medical or general)-psychiatric)

0134(Semi-private 3 and 4 beds-psychiatric)

0144(Private (deluxe)-psychiatric)

0154(Room & Board ward (medical or general)-psychiatric)

0204(Intensive care-psychiatric);

❖ <u>Provider specialty: The codes are different by claims sources</u>
o Medicare—NCH, DME hcfaspec

26(Psychiatry)

27(Geriatric psychiatry)

62(Psychologist)

68(Clinical psychologist)

86(Neuropsychiatry);

o Medicaid- PROV_SPEC

011 - Psychiatric          011 - Psychiatric

112 - Psychologist        112 - Psychologist

339 - Psychiatrist         339 - Psychiatrist

899 - Psychologist Group       899 - Psychologist Group

o Humana- Provider Spcty

103T00000X    103T00000X    Psychologist

103TA0400X    103TA0400X    Psychologist Addiction-Substance Use

103TA0700X    103TA0700X    Psychologist Adult Development & Aging

103TB0200X    103TB0200X    Psychologist Behavioral

103TC0700X    103TC0700X    Psychologist Clinical

103TC1900X    103TC1900X    Psychologist Counseling

103TC2200X    103TC2200X    Psychologist Child, Youth & Family

103TE1000X    103TE1000X    Psychologist Educational

103TE1100X    103TE1100X    Psychologist Exercise & Sports

103TF0000X    103TF0000X    Psychologist Family

103TF0200X    103TF0200X    Psychologist Forensic

102L00000X    102L00000X    PSYCHOANALYST

103G00000X    103G00000X    Neuropsychologist

103GC0700X    103GC0700X    Neuropsychologist Clinical

103TH0100X    103TH0100X    Psychologist Health

103TM1700X    103TM1700X    Psychologist Men & Masculinity

103TM1800X    103TM1800X    Psychologist Mental Retardation & Dev

103TP0814X    103TP0814X    Psychologist Psychoanalysis

103TP2700X    103TP2700X    Psychologist Psychotherapy

103TP2701X    103TP2701X    Psychologist Psychotherapy, Group

103TR0400X    103TR0400X    Psychologist Rehabilitation

103TS0200X    103TS0200X    Psychologist School

103TW0100X    103TW0100X    Psychologist Women

163WP0808X    163WP0808X    Reg Nurse Psych/Mental Health

163WP0809X    163WP0809X    Reg Nurse Psych/Mental Health-Adult

167G00000X    167G00000X    Licensed Psychiatric Technician

1835P1300X    1835P1300X    Pharmacist Psychopharmacy

2084A0401X    2084A0401X    Psychiatry & Neurology Addiction Medicin

2084B0002X    2084B0002X    BARIATRIC MEDICINE

2084D0003X    2084D0003X    DIAGNOSTIC NEUROIMAGING

2084F0202X    2084F0202X    Psychiatry & Neurology Forensic Psychiat

2084N0400X    2084N0400X    Psychiatry & Neurology

2084N0402X    2084N0402X    Psychiatry & Neurology Child Neuro

2084N0600X    2084N0600X    Psychiatry & Neurology Clinical Neurophy

2084P0005X    2084P0005X    Psychiatry & Neurology Neurodevelopment

2084P0015X    2084P0015X    PSYCHOSOMATIC MEDICINE

2084P0800X    2084P0800X    Psychiatry & Neurology Psychiatry

2084P0802X    2084P0802X    Psychiatry & Neurology Addiction Psych

2084P0804X    2084P0804X    Psychiatry & Neurology Child & Adolesc

2084P0805X    2084P0805X    Psychiatry & Neurology Geriatric Psych

2084P2900X    2084P2900X    Psychiatry & Neurology Pain Medicine

2084S0010X    2084S0010X    Psychiatry & Neurology Sports Medicine

2084V0102X    2084V0102X    Psychiatry & Neurology Vascular Neurolog

273R00000X    273R00000X    Psychiatric Unit

283Q00000X    283Q00000X    Psychiatric Hospital

323P00000X    323P00000X    Psychiatric Residential Treatment Fac

363LP0808X    363LP0808X    Nurse Practitioner Psych/Mental Health

364SP0808X    364SP0808X    Clinical Nurse Spec Psych/Mental

364SP0809X    364SP0809X    Clinical Nurse Spec Psych/Mental Adult

364SP0810X    364SP0810X    Clin Nurse Spec Psych/Mental Child-Fam

364SP0811X    364SP0811X    Clin Nurse Spec Psych/Mental Chron Ill

364SP0812X    364SP0812X    Clin Nurse Spec Psych/Mental Community

364SP0813X    364SP0813X    Clin Nurse Spec Psych/Mental Geropsych


oAnthem-- HCIProvSpec

26 psychiatry;


❖ CPT codes:

90804–90829

90845: Under Psychotherapy for Crisis Services and Procedures.

90847: Family psychotherapy (conjoint psychotherapy) (with patient present)

90849: Multiple-family group psychotherapy

90853: Group psychotherapy (other than of a multiple family group)

90857: Interactive group psychotherapy

90865: Under Other Psychiatric Services or Procedures.

90870: Under Other Psychiatric Services or Procedures

G0409: Social work and psychological services, directly relating to and/or furthering the patient's rehabilitation goals, each 15 minutes, face-to-face; individual (services provided by a corf-qualified social worker or psychologist in a corf).

G0410: Group psychotherapy other than of a multiple-family group, in a partial hospitalization setting, approximately 45 to 50 minutes

G0411: Interactive group psychotherapy, in a partial hospitalization setting, approximately 45 to 50 minutes.

❖ Antidepressant Usage (Identified by using National Drug Codes)

Variables included:

- o Depression status
- o County
- o Census Tract
- o Race
- o Smoking status (both kcr and augmented)
- o Marital Status
- o County Beale code
- o Urban/Rural status
- o Insurance Type
- o Appalachian status
- o Age at diagnosis
- o Year of Diagnosis
- o Diagnostic Confirmation
- o Class of Case
- o ER, PR and HER2 status (csfactor1-16 http://web2.facs.org/cstage0205/breast/Breastschema.html)
- o Best Stage
- o Tumor Size
- o Grade
- o Histology code
- o Behavior code
- o Sequence number
- o First course treatment (FstTrtCompCode)
- o Surgery code (RXSummSurgPrimSite)
- o Radiation Therapy: Yes or no (both KCR and augmented, same for chemo, horm and surg)
- o Chemotherapy: Yes or no
- o Hormonal Therapy: Yes or no

- o Carlson Comorbidity Index score (CCI, if do not have 12 months continuous enroll and no claims information then consider as missing)
- o Survival status(vitalstat)
- o Follow-up time(survival_month)
- o County education and below poverty status

Index:

- o 14 months continuous enroll: 1 month prior to 12 months after
- o 13 months continuous enroll: month of diagnosis to 12 months after
- o 12 months continuous enroll: 12 months prior cancer diagnosis
- o Subsequent cancer within 1 year
- o Smoking 12 months: capture smoking status using claims 12 months prior cancer diagnosis
- o Smoking 25 months: capture smoking status using claims 12 months prior and 12 months after

## Breast Cancer Guideline Treatment Algorithm

The treatment available in KCR:

Surgery, Chemotherapy, Radiation, Immunotherapy, Hormone therapy, except Surgery, most other therapy known as Yes or NO with a starting date.

**Stage 0:**

Main treatment (one of the following)

- Lumpectomy + followed irradiation +hormone therapy
- Mastectomy

**Stage I&II:**

Main treatment (one of the following)

- Lumpectomy + followed irradiation
- Mastectomy.

Additional treatment

- If patients have hormone receptor-positive (ER-positive or PR-positive) breast cancer, hormone therapy is included as standard care, and whether to receive chemotherapy depends on genomic analysis of the tumor (such as OncotypeDX). Since OncotypeDX is not available in standard KCR data, hormone therapy will be considered as standard care for ER, PR positive.
- If the cancer is HER2-positive, treatment with trastuzumab (Immunotherapy) should be given.
- If the cancer is not hormone receptor-positive, chemotherapy is given.

**Stage III:**

Main treatment (one of the following)

- Begin with any neoadjuvant therapy {Chemotherapy, and/or hormone therapy, and/or trastuzumab (immunotherapy), followed with lumpectomy/mastectomy, followed radiation
- Begin with surgery. Followed with Mastectomy + adjuvant chemotherapy, and/or hormone therapy, and/or trastuzumab (immunotherapy).

Additional treatment

- If patients have hormone receptor-positive (ER-positive or PR-positive, HER2 negative) breast cancer, hormone therapy is included as standard care.
- If the cancer is HER2-positive, treatment with trastuzumab (Immunotherapy) should be given.

**Stage IV:**

- Hormone receptor-positive and HER2 negative cancers: hormone therapies are used for as long as possible before chemotherapy is introduced
- HER2-positive cancers: Trastuzumab/Herceptin (Immunotherapy is given along with chemothrepy)
- Hormone receptor-negative cancers: Chemotherapy is the main treatment.
- How about surgery or radiation?

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## *SAS CODES*

## Creating Formats for Categorical Variables

```
proc format lib=out.formats;
value appalf
      0="Non-Appal"
      1="Appal";
value smokerf
      0="Non-smoker"
        1='Smoker'
        9='Unknown';
value stagef
      0="Stage 0"
        1='Stage I'
        2="Stage II"
        3="stage III"
        4="Stage IV"
        9='Unknown,N/A';
value seqcasef
      0="No"
        1="Yes";
value indicatorf
      0="No"
        1="Yes"
      9='Unknown';
value treatclaimf
      1='Yes';
value treatkcrf
      1='Yes';
value chalsonf
      -1='Missing'
        0="0"
        1="1"
        2=">=2";
value hormonef
      -1='Missing'
      1='Positive/Elevated'
      2='Negative'
        9='Unknown';
value tumorsizef
      -1='Missing'
        1="<2"
        2="2-<5"
        3=">=5"
      9='Unknown,N/A';
value agef
      1='21-49'
        2='50-65'
        3='65-74'
        4='75+';

value diagconf
      1='Histology'
        2='Imaging/Clinical'
        9='Unknown';
```

```
value $ firsttreatmentf
     0='No Definitive Therapy or Surgery at Regional and/or Distant Sites
only'
     1='Surgery at Primary Site Only'
     2='Chemotherapy Only'
     3='Surgery at Primary Site/Chemotherapy'
     4=' Radiation Therapy Only'
     5='Surgery at Primary Site/Radiation Therapy'
     6='Chemotherapy/Radiation Therapy'
     7='Surgery at Primary Site/Chemo/Radiation Therapy'
     8='Other Therapy Only'
     9='Surgery at Primary Site/Other Therapy'
     10='Chemotherapy/Other Therapy'
     11='Surgery at Primary Site/Chemo/Other Therapy'
     12='Radiation/Other Therapy'
     13='Surgery at Primary Site/Radiation/Other Therapy'
     14='Chemo/Radiation/Other Therapy'
     15='Surgery at Primary Site/Chemo/Radiation/Other Therapy'
     64='Unknown if or what therapy received';
value gradef
     1='Well'
       2='Moderate'
       3='Poorly/Undifferentiated'
     9='Unknown';
value maritalf
     1='Married'
       2='Never Married'
       3='Separated/Divorced/Widowed'
     9='Unknown';
value metrof
     0='Non-metro'
       1='Metro';
value pcharlsonf
     -1='Missing'
       0="0"
       1="1"
       2=">=2";
value racef
     1='White'
       2='Non-white'
       9='Unknown';
value surgerytypef
     0='NO'
       1='Mastectomy'
       2='Lumpectomy'
     9='Unknown';
value urbanf
     1='Urban'
       0='Rural';
value vitalstatf
     0='Dead'
     1='Alive';
value $ tobaccof
     0="Non-smoker"
       1='Smoker'
       9='Unknown';
```

```
value highschoolf
     1='<65%'
       2='65%-<75%'
       3='75%-<85%'
     4='>=85%'
     9='Unknown';
value povertyf
     1='<5%'
       2='5%-<10%'
       3='%10-<20%'
       4='>=20%'
     9='Unknown';
value newmetrof
     1='Metro'
       2='Rural'
       3='Isolated';
value stagegrpf
     0='Stage 0'
     1='Stage I&II'
       2='Stage III&IV'
       9='Unknown,N/A';
value cancertreatmentf
     0='No'
       1='Yes'
       9='unknown';
value depressionf
     0='No depression'
     1='Pre&Pro depresion'
       2='Pre depression only'
       3='Post depression only'
       9='Unknown';
value insurancef
     0='No insurance'
       1="Medicare"
       2='Medicaid/Other Public'
       3='Private insurance'
       9='Unknown';
run;
```

## Format Assignment

```
options fmtsearch=(in.formats);

data in.breast_capstonewithformat;
set in.breast_capstone;
format appal appalf.
        AUGMENTED_FINALSMOKE_12M smokerf.
          AUGMENTED_FINALSMOKE_25M smokerf.
          STAGE stagef.
          CENT_TIME_A  indicatorf.
          CENT_TIME_B  indicatorf.
          CHEMO_AUGMENTED indicatorf.
          CHEMO_KCR treatkcrf.
          CHARLSONGRP chalsonf.
          ER hormonef.
          PR hormonef.
          HER2  hormonef.
          TUMORSIZE tumorsizef.
          DEPRESSION_STATUS indicatorf.
          DEP_TIME_A indicatorf.
          DEP_TIME_B indicatorf.
          DIAGAGEGRP agef.
          DIAGCONFIRMGRP diagconf.
          DRUG_TIME_A indicatorf.
        DRUG_TIME_B indicatorf.
        ENROLL_14MON indicatorf.
          FSTTRTCOMPCODE firsttreatmentf.
          GRADE gradef.
          HCPCS_TIME_A indicatorf.
        HCPCS_TIME_B indicatorf.
          psychotherapy_TIME_A indicatorf.
        psychotherapy_TIME_B indicatorf.
        HORM_AUGMENTED indicatorf.
          HORM_KCR treatkcrf.
          INDEX_1CLAIM indicatorf.
          INDEX_ENROLL_12PRIOR indicatorf.
        INDEX_ENROLL_13AFTER indicatorf.
          INDEX_SUBSEQCASE indicatorf.
          MARITALGRP maritalf.
          METRO metrof.
          PCHARLSONGRP pcharlsonf.
        PROVD_TIME_A indicatorf.
        PROVD_TIME_B indicatorf.
          RACE racef.
        RAD_AUGMENTED indicatorf.
          RAD_KCR treatkcrf.
          SURGERYTYPE surgerytypef.
        SURG_AUGMENTED indicatorf.
          SURG_KCR treatkcrf.
          TOBACCO tobaccof.
          TREAT_CENT indicatorf.
        TREAT_HCPCS indicatorf.
        TREAT_NDC  indicatorf.
        TREAT_PROVD indicatorf.
```

```
     URBAN urbanf.
       VITALSTAT vitalstatf.
       highschool_or_more highschoolf.
       below_poverty povertyf.
       new_metro newmetrof.;
run;
```

## Merging Census Tract Related Information with Primary Data

```
PROC IMPORT OUT= WORK.census_tract
            DATAFILE= "Z:\FeiTong Lei\Capstone\depression breast cancer\
depression breast cancer\tract,patient_id.xlsx"
            DBMS=EXCEL REPLACE;
    RANGE="Sheet1$";
    GETNAMES=YES;
    MIXED=NO;
    SCANTEXT=YES;
    USEDATE=YES;
    SCANTIME=YES;
RUN;


libname in 'Z:\FeiTong Lei\Capstone\depression breast cancer\Data';


proc sort data=census_tract;
by patient_id;
run;

proc sort data=in.breast_capstonewithformat;
by patient_id;
run;


data in.allcases;
merge census_tract in.breast_capstonewithformat;
by patient_id;
run;


******************MERGE INCOME AND EDUCATION INFORMATION BY CENSUS TRACT****;
data capstone_allcases;
set in.allcases;
GEOID=cat(county,tract);
run;
```

```
libname ct 'Z:\FeiTong Lei\Medicare\Data\Census Tract\updated_datasets';
 data kyct2000;
 set ct.kyct2000;
 GEOID=cat(state,county,tract);
 keep GEOID CTMED POV_TOT HS_TOT;
 run;
 proc sort data=capstone_allcases;
 by GEOID;
 run;
 proc sort data=kyct2000;
 by GEOID;
 run;
 data in.capstone_allcases;
 merge capstone_allcases kyct2000;
 by GEOID;
 run;
```

## Data Cleaning and Data Management

```
libname in 'Z:\FeiTong Lei\Capstone\depression breast cancer\Data';
options fmtsearch=(in.formats);

data primarycases;
set in.capstone_allcases;
where centralsequencenumber in (0,1);
run;

proc format;
value depressionf
      0='No depression'
      1='Pre&Pro depresion'
        2='Pre depression only'
        3='Post depression only'
        9='Unknown';
run;


*************Data complementary******;

data primarycases;
set primarycases;

*********Creat a variable to indicate time recived
psychotherapy before or after cancer diagnosis****;
if cent_time_a=1 or hcpcs_time_a=1 or provd_time_a=1 then
psychotherapy_time_a=1;

if cent_time_b=1 or hcpcs_time_b=1 or provd_time_b=1 then
psychotherapy_time_b=1;


*******Creat a variable to indicate whethere psychotherapy recieved**;
if Treat_cent=1 or treat_hcpcs=1 or treat_provd=1 then treat_psychotherapy=1;

******Stage Group***********;
```

```
if beststagegrp ge 0 and beststagegrp lt 10 then stage = 0;
else if beststagegrp ge 10 and beststagegrp lt 30 then stage=1;
else if beststagegrp ge 30 and beststagegrp lt 50 then stage=2;
else if beststagegrp ge 50 and beststagegrp lt 70 then stage=3;
else if beststagegrp ge 70 and beststagegrp le 80 then stage=4;
else if beststagegrp in (88,99) then stage=9;
*********Early Stage or else****;
if stage in (1,2) then stagegrp =1;
else if stage in (3,4) then stagegrp=2;
else if stage in(0) then stagegrp=0;
else stagegrp =9;
******tumorsize*********;
if cstumorsize in (998,999) then tumorsize=9;
else if cstumorsize ge 0 and cstumorsize lt 200 then tumorsize=1;
else if cstumorsize ge 200 and cstumorsize lt 500 then tumorsize=2;
else if cstumorsize in (990,991,992,996,997) then tumorsize=1;
else if cstumorsize in (993,994,995) then tumorsize=2;
else if cstumorsize ge 500 and cstumorsize le 989 then tumorsize=3;
else tumorsize=-1;
*********Charlson index***;
if chrlson =0 then charlsongrp=0;
else if chrlson = 1 then charlsongrp=1;
else if chrlson ge 2 then charlsongrp=2;
else charlsongrp=-1;
***********ER Status******;
if csfactor1 in (10) then ER=1;
else if csfactor1 in (20) then ER=2;
else if csfactor1 in (30,996,997,998,999) then ER=9;

***********PR Status******;
if csfactor2 in (10) then pr=1;
else if csfactor2 in (20) then pr=2;
else if csfactor2 in (30,996,997,998,999) then pr=9;

******Hormone receptor status****;
if er = 1 or pr =1 then Hormone_receptor =1;
else if er =2 and pr=2 then Hormone_receptor=2;
else Hormone_receptor=9;

***********HER2 Status******;
if csfactor15 in (10) then HER2=1;
else if csfactor15 in (20) then HER2=2;
else if csfactor15 in (30,996,997,998,999) then HER2=9;
else HER2=-1;
********Diagnostic age group****;
if diagage gt 0 and diagage le 49 then DIAGAGEGRP=1;
else if diagage ge 50 and diagage le 64 then diagagegrp=2;
else if diagage ge 65 and diagage le 74 then diagagegrp=3;
else if diagage ge 75 then diagagegrp=4;

*******Diagconfirmation*****;
if diagconfirm in (1,3) then diagconfirmgrp=1;
else if diagconfirm in (2,4,5,6,7,8) then diagconfirmgrp=2;
else if diagconfirm in (9) then diagconfirmgrp=9;

*******Marital group*******;
```

```
if maritalstatus in (2,6) then maritalgrp=1;
else if maritalstatus in (1) then maritalgrp=2;
else if maritalstatus in (3,4,5) then maritalgrp=3;
else if maritalstatus in (9) then maritalgrp =9;

*********Prior Charlson score******;
if pchrlson =0 then pcharlsongrp=0;
else if pchrlson = 1 then pcharlsongrp=1;
else if pchrlson ge 2 then pcharlsongrp=2;
else pcharlsongrp= -1;

********Race*******;
if race1 in (1,3) then race =1;
else if race1 in (2,4,5,6,8,10,15,16,96,98,97) then race=2;
else if race1 in(99) then race =9;
********Grade*******;
if grade =1 then gradegrp=1;
else if grade=2 then gradegrp=2;
else if grade in(3,4 )then gradegrp=3;
else gradegrp=9;
******Surgery type******;
if rxsummsurgprimsite in (0) then surgerytype =0;
else if rxsummsurgprimsite ge 20 and rxsummsurgprimsite lt 30 then
surgerytype =2;
else if rxsummsurgprimsite ge 30 and rxsummsurgprimsite le 80  then
surgerytype =1;
else if rxsummsurgprimsite in (90,99) then surgerytype =9;
******Below high school******;
if hs_tot  ge 0 and hs_tot lt 65 then highschool_or_more=1;
else if hs_tot ge 65 and hs_tot lt 75 then highschool_or_more=2;
else if hs_tot ge 75 and hs_tot lt 85 then highschool_or_more=3;
else if hs_tot ge 85 then highschool_or_more=4;
else highschool_or_more=9;
******Below Poverty*********;
if pov_tot ge 0 and pov_tot lt 5 then below_poverty=1;
else if pov_tot ge 5 and pov_tot lt 10 then below_poverty=2;
else if pov_tot ge 10 and pov_tot lt 20 then below_poverty=3;
else if pov_tot ge 20  then below_poverty=4;
else below_poverty=9;
********Metro,rural status****;
if beale_code03 in (1,2,3) then new_metro=1;
else if beale_code03 in (4,5,6) then new_metro=2;
else if beale_code03 in (7,8,9) then new_metro=3;

************Time before cancer diagnosis(NO/Unknown)******;
if dep_time_b ne 1 and index_enroll_12prior=1 then dep_time_b=0;
else if dep_time_b ne 1 and index_enroll_12prior ne 1 then dep_time_b=9;

if psychotherapy_time_b ne 1 and index_enroll_12prior =1 then
psychotherapy_time_b=0;
else if psychotherapy_time_b ne 1 and  index_enroll_12prior ne 1 then
psychotherapy_time_b=9;

if drug_time_b ne 1 and index_enroll_12prior =1 then drug_time_b=0;
else if drug_time_b ne 1 and  index_enroll_12prior ne 1 then drug_time_b=9;
```

```
*******Time after cancer diagnosis(NO/Unknown)********;
if dep_time_a ne 1 and index_enroll_13after=1 then dep_time_a=0;
else if dep_time_a ne 1 and index_enroll_13after ne 1 then dep_time_a=9;


if psychotherapy_time_a ne 1 and index_enroll_13after=1 then
psychotherapy_time_a=0;
else if psychotherapy_time_a ne 1 and index_enroll_13after ne 1 then
psychotherapy_time_a=9;
else if psychotherapy_time_a ne 1 then psychotherapy_time_a=9;


if drug_time_a ne 1 and index_enroll_13after=1 then drug_time_a =0;
else if drug_time_a ne 1 and index_enroll_13after ne 1 then drug_time_a=9;
else if drug_time_a  ne 1 then drug_time_a =9;

if psychotherapy_time_a=1 or drug_time_a=1 then depression_trt_after=1;
else if psychotherapy_time_a=0 and drug_time_a =0 then
depression_trt_after=0;
else depression_trt_after=9;

******depression status(no/unknown)***;
if dep_time_b =0 and dep_time_a=0 then depression_status=0;
else if depression_status ne 1 then depression_status=9;

*********Cancer treatment********;
if chemo_augmented=1 then chemo=1;
else if chemo_augmented ne 1 and  index_enroll_13after=1 then chemo=0;
else if chemo_augmented ne 1  and index_enroll_13after ne 1 then chemo=9;

if horm_augmented=1 then horm=1;
else if horm_augmented ne 1 and  index_enroll_13after=1 then horm=0;
else if horm_augmented ne 1  and index_enroll_13after ne 1 then horm=9;

if rad_augmented=1 then rad=1;
else if rad_augmented ne 1 and  index_enroll_13after=1 then rad=0;
else if rad_augmented ne 1  and index_enroll_13after ne 1 then rad=9;

if surg_augmented=1 then surg=1;
else if surg_augmented ne 1 and  index_enroll_13after=1 then surg=0;
else if surg_augmented ne 1  and index_enroll_13after ne 1 then surg=9;


*******Ceate a variable to indicate whether cancer treatment is
appropriate****;
*******For hormone receptor status******;
/*if SURVIVAL_MONTH le 6 then appropriate_cancertreatment=-1;
else if SURVIVAL_MONTH gt 6 then do;*/

if hormone_receptor =1 and horm=1  then horm_standard=1;

else if hormone_receptor=1 and horm=0 then horm_standard=0;
else if hormone_receptor=2 and horm=1 then horm_standard=0;
else if hormone_receptor=2 and horm=0 then horm_standard=1;
else horm_standard=9;
```

```
*******For stage 0*******;
if stage=0 and surgerytype=1 then surg_standard=1;
else if stage=0 and surgerytype=2 and rad=1 then surg_standard=1;
else if stage=0 and surgerytype=2 and rad=0 then surg_standard=0;
else if stage=0 and surgerytype=2 and rad=9 then surg_standard=9;
else if stage=0 and surgerytype=0 then surg_standard=0;
else if stage=0 and surgerytype=9 then surg_standard=9;

if stage=0 and surg_standard=1 and horm_standard=1 then
appropriate_cancertreatment=1;
else if stage=0 and (surg_standard=0 or horm_standard=0) then
appropriate_cancertreatment=0;
else if stage=0 and surg_standard=1 and horm_standard=9 then
appropriate_cancertreatment=9;
else if stage=0 and surg_standard=9 and horm_standard=1 then
appropriate_cancertreatment=9;

************For stage I&II********;
if stage in (1,2) and surgerytype=0 then surg_standard=0;
else if stage in (1,2) and surgerytype=1 then surg_standard=1;
else if stage in (1,2) and surgerytype=2 and rad=1 then surg_standard=1;
else if stage in (1,2) and surgerytype=2 and rad=0 then surg_standard=0;
else if stage in (1,2) and surgerytype=2 and rad=9 then surg_standard=9;
else if stage in (1,2) and surgerytype=9 then surg_standard=9;

if stage in (1,2) and hormone_receptor=9 then chemo_standard=9;
else if  stage in (1,2) and hormone_receptor=2 and chemo=1 then
chemo_standard=1;
else if  stage in (1,2) and hormone_receptor=2 and chemo=0 then
chemo_standard=0;
else if  stage in (1,2) and hormone_receptor=2 and chemo=9 then
chemo_standard=9;
else if  stage in (1,2) and hormone_receptor=1 then chemo_standard=1;
else if  stage in (1,2) and hormone_receptor=9 then
chemo_standard=9;*******To be discussed*****;


if stage in (1,2) then do;
if surg_standard=1 and horm_standard=1 and chemo_standard=1 then
appropriate_cancertreatment=1;
else if surg_standard=0 or horm_standard=0 or chemo_standard=0 then
appropriate_cancertreatment=0;
else if surg_standard=9 or horm_standard=9 or chemo_standard=9 then
appropriate_cancertreatment=9;
end;

*********For stage III************;
****Begin with neoneoadjuvant therapy***;

if stage=3 then do;
*if chemo=1 and surg=1 and datesurg1 < datechemo1 and surgerytype =2 then
surg_standard=0;
if surg=1 then surg_standard=1;
else if surg=0 then surg_standard=0;
else if surg=9 then surg_standard=9;
```

```
if chemo=0 then chemo_standard=0;
else if chemo=1 then chemo_standard=1;
else if chemo=9 then chemo_standard=9;

if rad=0 then rad_standard=0;
else if rad=1 then rad_standard=1;
else if rad=9 then rad_standard=9;


if surg_standard=1 and horm_standard=1 and chemo_standard=1 and
rad_standard=1 then appropriate_cancertreatment=1;
else if surg_standard=0 or horm_standard=0 or chemo_standard=0 or
rad_standard=0 then appropriate_cancertreatment=0;
else if surg_standard=9 or horm_standard=9 or chemo_standard=9 or
rad_standard=9 then appropriate_cancertreatment=9;

end;

******For stage IV**********;
if  stage =4 and hormone_receptor=2 and chemo=1 then chemo_standard=1;
else if  stage =4 and hormone_receptor=2 and chemo=0 then chemo_standard=0;
else if stage =4 and hormone_receptor=1 then chemo_standard=1;

if stage=4 and horm_standard=1 and chemo_standard=1 then
appropriate_cancertreatment=1;
else if stage =4 and ( horm_standard=0 or chemo_standard=0) then
appropriate_cancertreatment=0;
else if stage=4 then appropriate_cancertreatment=9;

********Stage unknown******;
if stage=9 then appropriate_cancertreatment=9;

label csfactor1='ER Status'
      csfactor2='PR status'
      csfactor3='HER2 Status'
      dep_time_b='Depression diagnosed before cancer';
/*end;*/

*******new category of depression****;
if dep_time_b=0 and dep_time_a=0 then depression=0;
else if dep_time_b=1 and dep_time_a=1 then depression=1;
else if dep_time_b=1 and dep_time_a=0 then depression=2;
else if dep_time_b=0 and dep_time_a=1 then depression=3;
else if dep_time_b =9 or dep_time_a=9 then depression=9;

**********Insurance type************;
if primarypayor in (1,2) then insurance_type=0;
else if primarypayor in (10,99) then insurance_type=9;
else if primarypayor in (60,61,62,63,64) then insurance_type=1;
else if primarypayor in (31,35,65,66,67,68) then insurance_type=2;
else if primarypayor in (20, 21) then insurance_type=3;


format highschool_or_more highschoolf. new_metro newmetrof. stagegrp
stagegrpf. gradegrp gradef.
```

```
depression_trt_after indicatorf. appropriate_cancertreatment
cancertreatmentf.  diagagegrp agef.
Hormone_receptor hormonef. chemo horm surg rad indicatorf. chemo_standard
horm_standard surg_standard rad_standard indicatorf. depression depressionf.
insurance_type insurancef.;
run;


data in.analysis;
set primarycases;
run;

proc freq data=primarycases;
table  appropriate_cancertreatment ;
run;




data depression;
set primarycases;
where depression ^in (9) and stage ^ in (0);
run;


proc freq data=fullenrollment;
table appropriate_cancertreatment  ;
run;
```

## Comparison between Patients Group Based on Depression Status

```
libname in 'C:\Users\walala\Desktop\Capstone\depression breast cancer\Data';
options fmtsearch=(in.formats);

ods pdf file='Z:\FeiTong Lei\Capstone\depression breast
cancer\output\patients_character.pdf';


data depression;
set in.analysis;
where depression in (0,1,2,3)and stage in (1,2,3,4,9);
format race racef.;
run;

data depression_a;
set in.analysis;
where dep_time_a in (0,1)and stage in (1,2,3,4,9);
format race racef.;
run;


%macro sec(var);

proc freq data=fullenrollment;
table &var*depression/chisq;
```

```
where depression in (1,2);
run;

%mend;
%sec(RACE);
%sec(AUGMENTED_FINALSMOKE_12M);
%sec(DIAGAGEGRP);
%sec(APPAL);
%sec(MARITALGRP);
%sec(highschool_or_more);
%sec(below_poverty);
%sec(insurance_type);
%sec(CHARLSONGRP);
%sec(stage);
%sec(gradegrp);
%sec(Tumorsize);
%sec(appropriate_cancertreatment);

******Standard Treatment*****;
%macro sec(var);

proc freq data=in.fullenrollment;
table &var*appropriate_cancertreatment/chisq;
where appropriate_cancertreatment in (0,1);
run;

%mend;
%sec(RACE);
%sec(AUGMENTED_FINALSMOKE_12M);
%sec(DIAGAGEGRP);
%sec(APPAL);
%sec(MARITALGRP);
%sec(highschool_or_more);
%sec(below_poverty);
%sec(insurance_type);
%sec(CHARLSONGRP);
%sec(stage);
%sec(gradegrp);
%sec(Tumorsize);
%sec(depression);




*********Depression after Cancer*****;

%macro sec(var);

proc freq data=depression;
table depression*&var/chisq;
where depression in (0,3);

run;
%mend;
%sec(AUGMENTED_FINALSMOKE_12M);
%sec(APPAL);
```

```
%sec(new_metro);
%sec(DIAGAGEGRP);
%sec(MARITALGRP);
%sec(STRATA);
%sec(CHARLSONGRP);
%sec(Hormone_receptor);
%sec(HER2);
%sec(STAGE);
%sec(RACE);
%sec(highschool_or_more);
%sec(below_poverty);
```

## Logistic Regression and Cox Regression

```
PROC LOGISTIC data=in.fullenrollment;
class appropriate_cancertreatment(ref='Yes') DEP_TIME_B(REF='No')
DEP_TIME_A(REF='No') depression_status(ref='No')depression(ref='No
depression') AUGMENTED_FINALSMOKE_12M(ref="Non-smoker") APPAL (ref="Non-
Appal")
      urban(ref='Urban') Metro(ref='Metro') DIAGAGEGRP(ref='21-49')
MARITALGRP(ref='Married') RACE(ref='Non-white') STRATA (ref='1')
CHARLSONGRP(ref="0")
      PCHARLSONGRP(ref="0") ER(ref='Positive/Elevated')
PR(ref='Positive/Elevated') GRADEgrp(ref='Poorly/Undifferentiated')
HER2(ref='Positive/Elevated')STAGE(ref="Stage I")
      TUMORSIZE(ref="<2") highschool_or_more(ref='>=85%')
below_poverty(ref='<5%')Hormone_receptor(ref='Positive/Elevated')
insurance_type(ref='Private insurance')/param=glm;
model appropriate_cancertreatment= depression APPAL  highschool_or_more
DIAGAGEGRP MARITALGRP  insurance_type
                        CHARLSONGRP hormone_receptor;
where appropriate_cancertreatment in (0,1);
run;


proc phreg data=fullenrollment;
class depression_status(ref='No') depression(ref='No depression') dep_time_a
(ref='No') dep_time_b(ref='No') AUGMENTED_FINALSMOKE_12M(ref="Non-smoker")
APPAL (ref="Appal")surg_augmented (ref='Yes')
      rad_augmented (ref='Yes') horm_augmented (ref='Yes') chemo_augmented
(ref='Yes')
      urban(ref='Urban') Metro(ref='Metro')  MARITALGRP(ref='Married')
RACE(ref='Non-white') STRATA (ref='1') CHARLSONGRP(ref="0")
      PCHARLSONGRP(ref="0") ER(ref='Positive/Elevated')
hormone_receptor(ref='Positive/Elevated') GRADEgrp(ref='Well')
HER2(ref='Positive/Elevated')
      TUMORSIZE(ref="<2") highschool_or_more(ref='>=85%')
below_poverty(ref='<5%')drug_time_a(ref='No') psychotherapy_time_a(ref='No')
new_metro(ref='Metro')
      appropriate_cancertreatment(ref='Yes') DIAGAGEGRP(ref='21-49')
drug_time_a(ref='No') psychotherapy_time_a(ref='No')depression_trt_after
(ref='No') STAGE(ref="Stage I")
```

```
        insurance_type(ref='Private insurance') /param=glm;
model Survival_month*Vitalstat(1)= depression APPAL  AUGMENTED_FINALSMOKE_12M
highschool_or_more  DIAGAGEGRP MARITALGRP  insurance_type
                        STAGE CHARLSONGRP hormone_receptor gradegrp
appropriate_cancertreatment  ;
run;
```

## *OUTPUTS*

### Table 1.  Patients Characteristics (n=6054)

| Factors | No depression (n=5212) | | Pre&Post depression (n=246) | | Pre depression only (n=221) | | Post-depression only (n=375) | | P-value |
|---|---|---|---|---|---|---|---|---|---|
| | N | Pct | N | Pct | N | Pct | N | Pct | |
| Race | | | | | | | | | 0.3906 |
| White | 4869 | 85.93 | 237 | 4.18 | 212 | 3.74 | 348 | 6.14 | |
| Non-white | 328 | 88.17 | 9 | 2.42 | 9 | 2.42 | 26 | 6.99 | |
| Unknown | 15 | 93.75 | 0 | 0.00 | 0 | 0.00 | 1 | 6.25 | |
| Smoking Status | | | | | | | | | <.0001 |
| Non-smoker | 2352 | 87.50 | 89 | 3.31 | 87 | 3.24 | 160 | 5.95 | |
| Smoker | 1797 | 82.54 | 121 | 5.56 | 94 | 4.32 | 165 | 7.58 | |
| Unknown | 1063 | 89.40 | 36 | 3.03 | 40 | 3.36 | 50 | 4.21 | |
| Age at Diagnosis | | | | | | | | | |
| 21-49 | 440 | 80.29 | 34 | 6.20 | 20 | 3.65 | 54 | 9.85 | <.0001 |
| 50-65 | 1042 | 80.90 | 85 | 6.60 | 62 | 4.81 | 99 | 7.69 | |
| 65-74 | 1920 | 86.96 | 78 | 3.53 | 73 | 3.31 | 137 | 6.20 | |
| 75+ | 1810 | 90.05 | 49 | 2.44 | 66 | 3.28 | 85 | 4.23 | |
| Appalachian Status | | | | | | | | | 0.9966 |
| Non-Appal | 3786 | 86.12 | 179 | 4.07 | 159 | 3.62 | 272 | 6.19 | |
| Appal | 1426 | 86.01 | 67 | 4.04 | 62 | 3.74 | 103 | 6.21 | |
| Marital Status | | | | | | | | | 0.0015 |
| Married | 2558 | 87.84 | 110 | 3.78 | 97 | 3.33 | 147 | 5.05 | |
| Never Married | 348 | 82.27 | 25 | 5.91 | 18 | 4.26 | 32 | 7.57 | |
| Separated/Divorced/Widowed | 2133 | 84.91 | 100 | 3.98 | 103 | 4.10 | 176 | 7.01 | |
| Unknown | 173 | 83.57 | 11 | 5.31 | 3 | 1.45 | 20 | 9.66 | |
| High school or more | | | | | | | | | 0.8217 |
| <65% | 1159 | 85.60 | 60 | 4.43 | 55 | 4.06 | 80 | 5.91 | |
| 65%-<75% | 1324 | 86.09 | 59 | 3.84 | 52 | 3.38 | 103 | 6.70 | |
| 75%-<85% | 1332 | 85.22 | 65 | 4.16 | 65 | 4.16 | 101 | 6.46 | |
| >=85% | 1383 | 87.31 | 62 | 3.91 | 49 | 3.09 | 90 | 5.68 | |
| Unknown | 14 | 93.33 | 0 | 0.00 | 0 | 0.00 | 1 | 6.67 | |
| Below poverty | | | | | | | | | 0.4112 |
| <5% | 906 | 87.96 | 36 | 3.50 | 37 | 3.59 | 51 | 4.95 | |
| 5%-<10% | 1317 | 85.91 | 73 | 4.76 | 53 | 3.46 | 90 | 5.87 | |
| %10-<20% | 1566 | 85.67 | 64 | 3.50 | 67 | 3.67 | 131 | 7.17 | |
| >=20% | 1409 | 85.50 | 73 | 4.43 | 64 | 3.88 | 102 | 6.19 | |
| Unknown | 14 | 93.33 | 0 | 0.00 | 0 | 0.00 | 1 | 6.67 | |

| Factors | No depression (n=5212) | | Pre&Post depression (n=246) | | Pre depression only (n=221) | | Post-depression only (n=375) | | P-value |
|---|---|---|---|---|---|---|---|---|---|
| | N | Pct | N | Pct | N | Pct | N | Pct | |
| Primary payer | | | | | | | | | <.0001 |
| No insurance | 7 | 87.50 | 1 | 12.50 | 0 | 0.00 | 0 | 0.00 | |
| Medicare | 3722 | 86.56 | 168 | 3.91 | 145 | 3.37 | 265 | 6.16 | |
| Medicaid/ Other Public | 266 | 77.10 | 33 | 9.57 | 28 | 8.12 | 18 | 5.22 | |
| Private insurance | 1141 | 87.23 | 42 | 3.21 | 42 | 3.21 | 83 | 6.35 | |
| Unknown | 76 | 81.72 | 2 | 2.15 | 6 | 6.45 | 9 | 9.68 | |
| Charlson Score | | | | | | | | | <.0001 |
| Missing | 217 | 97.31 | 1 | 0.45 | 0 | 0.00 | 5 | 2.24 | |
| 0 | 3075 | 87.91 | 111 | 3.17 | 102 | 2.92 | 210 | 6.00 | |
| 1 | 1132 | 84.41 | 62 | 4.62 | 53 | 3.95 | 94 | 7.01 | |
| >=2 | 788 | 79.44 | 72 | 7.26 | 66 | 6.65 | 66 | 6.65 | |
| Stage | | | | | | | | | 0.0032 |
| Stage I | 2473 | 87.35 | 108 | 3.81 | 98 | 3.46 | 152 | 5.37 | |
| Stage II | 1560 | 84.23 | 87 | 4.70 | 65 | 3.51 | 140 | 7.56 | |
| stage III | 588 | 83.40 | 34 | 4.82 | 28 | 3.97 | 55 | 7.80 | |
| Stage IV | 348 | 90.39 | 9 | 2.34 | 16 | 4.16 | 12 | 3.12 | |
| Unknown,N/A | 243 | 86.48 | 8 | 2.85 | 14 | 4.98 | 16 | 5.69 | |
| Grade | | | | | | | | | 0.2868 |
| Well | 1129 | 86.98 | 52 | 4.01 | 38 | 2.93 | 79 | 6.09 | |
| Moderate | 2172 | 85.92 | 101 | 4.00 | 96 | 3.80 | 159 | 6.29 | |
| Poorly/Undifferentiated | 1480 | 85.65 | 75 | 4.34 | 59 | 3.41 | 114 | 6.60 | |
| Unknown | 431 | 86.20 | 18 | 3.60 | 28 | 5.60 | 23 | 4.60 | |
| Tumor Size (cm) | | | | | | | | | 0.2088 |
| <2 | 4926 | 86.19 | 230 | 4.02 | 204 | 3.57 | 355 | 6.21 | |
| 2-<5 | 19 | 73.08 | 2 | 7.69 | 2 | 7.69 | 3 | 11.54 | |
| >=5 | 2 | 66.67 | 1 | 33.33 | 0 | 0.00 | 0 | 0.00 | |
| Unknown,N/A | 265 | 85.48 | 13 | 4.19 | 15 | 4.84 | 17 | 5.48 | |
| Standard Cancer Care | | | | | | | | | 0.1485 |
| No | 1523 | 86.05 | 69 | 3.90 | 79 | 4.46 | 99 | 5.59 | |
| Yes | 3256 | 85.93 | 161 | 4.25 | 122 | 3.22 | 250 | 6.60 | |
| unknown | 433 | 87.47 | 16 | 3.23 | 20 | 4.04 | 26 | 5.25 | |

## Table 2. Standard Treatment (n=5559)

| Factors | Nonguideline Treatment (n=1770) | | Guideline Treatment (n=3789) | | p-value |
|---|---|---|---|---|---|
| | N | Pct | N | Pct | |
| Depression | | | | | 0.0586 |
| No depression | 1523 | 31.8686 | 3256 | 68.13 | |
| Pre/Post Depression | 69 | 30 | 161 | 70.00 | |
| Pre-depression only | 79 | 39.3035 | 122 | 60.70 | |
| Post-depression only | 99 | 28.3668 | 250 | 71.63 | |
| Race | | | | | 0.0566 |
| White | 1655 | 31.8514 | 3541 | 68.15 | |
| Non-white | 115 | 32.7635 | 236 | 67.24 | |
| Unknown | 0 | 0 | 12 | 100.00 | |
| Smoking Status | | | | | <.0001 |
| Non-smoker | 793 | 31.4932 | 1725 | 68.51 | |
| Smoker | 607 | 29.4517 | 1454 | 70.55 | |
| Unknown | 370 | 37.7551 | 610 | 62.24 | |
| Age at Diagnosis | | | | | <.0001 |
| 21-49 | 77 | 14.6667 | 448 | 85.33 | |
| 50-65 | 227 | 18.7139 | 986 | 81.29 | |
| 65-74 | 535 | 26.1486 | 1511 | 73.85 | |
| 75+ | 931 | 52.4507 | 844 | 47.55 | |
| Appalachian Status | | | | | 0.5456 |
| Non-Appal | 1285 | 31.6113 | 2780 | 68.39 | |
| Appal | 485 | 32.4632 | 1009 | 67.54 | |
| Marital Status | | | | | <.0001 |
| Married | 677 | 24.681 | 2066 | 75.32 | |
| Never Married | 124 | 31.3131 | 272 | 68.69 | |
| Separated/Divorced/Widowed | 917 | 40.3432 | 1356 | 59.66 | |
| Unknown | 52 | 35.3741 | 95 | 64.63 | |
| High school or more | | | | | <.0001 |
| <65% | 356 | 29.3245 | 858 | 70.68 | |
| 65%-<75% | 516 | 36.9099 | 882 | 63.09 | |
| 75%-<85% | 469 | 32.3671 | 980 | 67.63 | |
| >=85% | 425 | 28.581 | 1062 | 71.42 | |
| Unknown | 4 | 36.3636 | 7 | 63.64 | |
| Below poverty | | | | | 0.0076 |
| <5% | 270 | 27.9214 | 697 | 72.08 | |
| 5%-<10% | 430 | 30.3672 | 986 | 69.63 | |
| %10-<20% | 575 | 34.2874 | 1102 | 65.71 | |
| >=20% | 491 | 32.9973 | 997 | 67.00 | |
| Unknown | 4 | 36.3636 | 7 | 63.64 | |
| Primary payer | | | | | <.0001 |
| No insurance | 2 | 25.00 | 6 | 75.00 | |

## Table 2. Standard Treatment (n=5559) (Cont.)

| Factors | Nonguideline Treatment (n=1770) | | Guideline Treatment (n=3789) | | p- value |
|---|---|---|---|---|---|
| | N | Pct | N | Pct | |
| Medicare | 1476 | 37.24 | 2487 | 62.76 | |
| Medicaid/Other Public | 90 | 27.61 | 236 | 72.39 | |
| Private insurance | 192 | 15.46 | 1050 | 84.54 | |
| Unknown | 10 | 50.00 | 10 | 50.00 | |
| Charlson Score | | | | | <.0001 |
| Missing | 64 | 32.4873096 | 133 | 67.51 | |
| 0 | 905 | 27.8290283 | 2347 | 72.17 | |
| 1 | 419 | 34.0650407 | 811 | 65.93 | |
| >=2 | 382 | 43.4090909 | 498 | 56.59 | |
| Stage | | | | | <.0001 |
| Stage I | 900 | 32.9067642 | 1835 | 67.09 | |
| Stage II | 444 | 24.6119734 | 1360 | 75.39 | |
| stage III | 355 | 51.0057471 | 341 | 48.99 | |
| Stage IV | 71 | 21.9135802 | 253 | 78.09 | |
| Grade | | | | | <.0001 |
| Well | 371 | 30.4597701 | 847 | 69.54 | |
| Moderate | 717 | 29.875 | 1683 | 70.13 | |
| Poorly/Undifferentiated | 541 | 32.9275715 | 1102 | 67.07 | |
| Unknown | 141 | 47.3154362 | 157 | 52.68 | |
| Tumor Size (cm) | | | | | 0.3778 |
| <2 | 1725 | 31.7153889 | 3714 | 68.28 | |
| 2-<5 | 9 | 39.1304348 | 14 | 60.87 | |
| >=5 | 2 | 66.6666667 | 1 | 33.33 | |
| Unknown, N/A | 34 | 36.1702128 | 60 | 63.83 | |

## Table 3. Multivariable logistic regression to identify the association between depression status and nonguideline cancer treatment.

| Variables | OR | | 95% CI | P-value |
|---|---|---|---|---|
| Depression Status | | | | 0.2815 |
|     Pre depression only | 1.379 | 0.992 | 1.918 | |
|     Post depression only | 0.964 | 0.736 | 1.263 | |
|     Pre & Post depression | 1.041 | 0.751 | 1.441 | |
|     No Depression | Ref | | | |
| Applachian Status | | | | 0.0269 |
|     Applachian | 1.232 | 1.024 | 1.482 | |
|     Non-Appalachian | Ref | | | |
| Age at Diagnosis | | | | <.0001 |
|     50-65 | 1.239 | 0.915 | 1.677 | |
|     65-74 | 1.872 | 1.352 | 2.592 | |
|     75+ | 5.929 | 4.252 | 8.266 | |
|     21-49 | Ref | | | |
| Marital Status | | | | 0.0015 |
|     Never Married | 1.361 | 1.054 | 1.757 | |
|     Seperated/Divorced/Widowed | 1.294 | 1.125 | 1.489 | |
|     Unknown | 1.275 | 0.858 | 1.894 | |
|     Married | Ref | | | |
| High School or more | | | | 0.0002 |
|     <65% | 0.827 | 0.653 | 1.048 | |
|     65%-<75% | 1.295 | 1.081 | 1.553 | |
|     75%-<85% | 1.124 | 0.942 | 1.341 | |
|     Unknown | 1.845 | 0.496 | 6.863 | |
|     >=85% | Ref | | | |
| Primary payer | | | | 0.0078 |
|     No insurance | 1.887 | 0.352 | 10.127 | |
|     Medicare | 1.474 | 1.144 | 1.9 | |
|     Medicaid/Other Public | 1.734 | 1.245 | 2.413 | |
|     Unknown | 1.845 | 0.496 | 6.863 | |
|     Private insurance | Ref | | | |
| Charlson Score | | | | <.0001 |
|     1 | 1.093 | 0.934 | 1.28 | |
|     >=2 | 1.58 | 1.325 | 1.884 | |
|     Missing | 1.375 | 0.953 | 1.985 | |
|     0 | Ref | | | |
| Stage | | | | <.0001 |
|     Stage II | 0.539 | 0.464 | 0.626 | |
|     Stage III | 1.96 | 1.619 | 2.372 | |
|     Stage IV | 0.386 | 0.285 | 0.522 | |
|     Stage I | Ref | | | |
| Hormone Receptor | | | | <.0001 |
|     Negative | 2.762 | 2.349 | 3.247 | |
|     Positive | Ref | | | |

**Figure 1. Survival curves in breast cancer patients grouped based on depression**
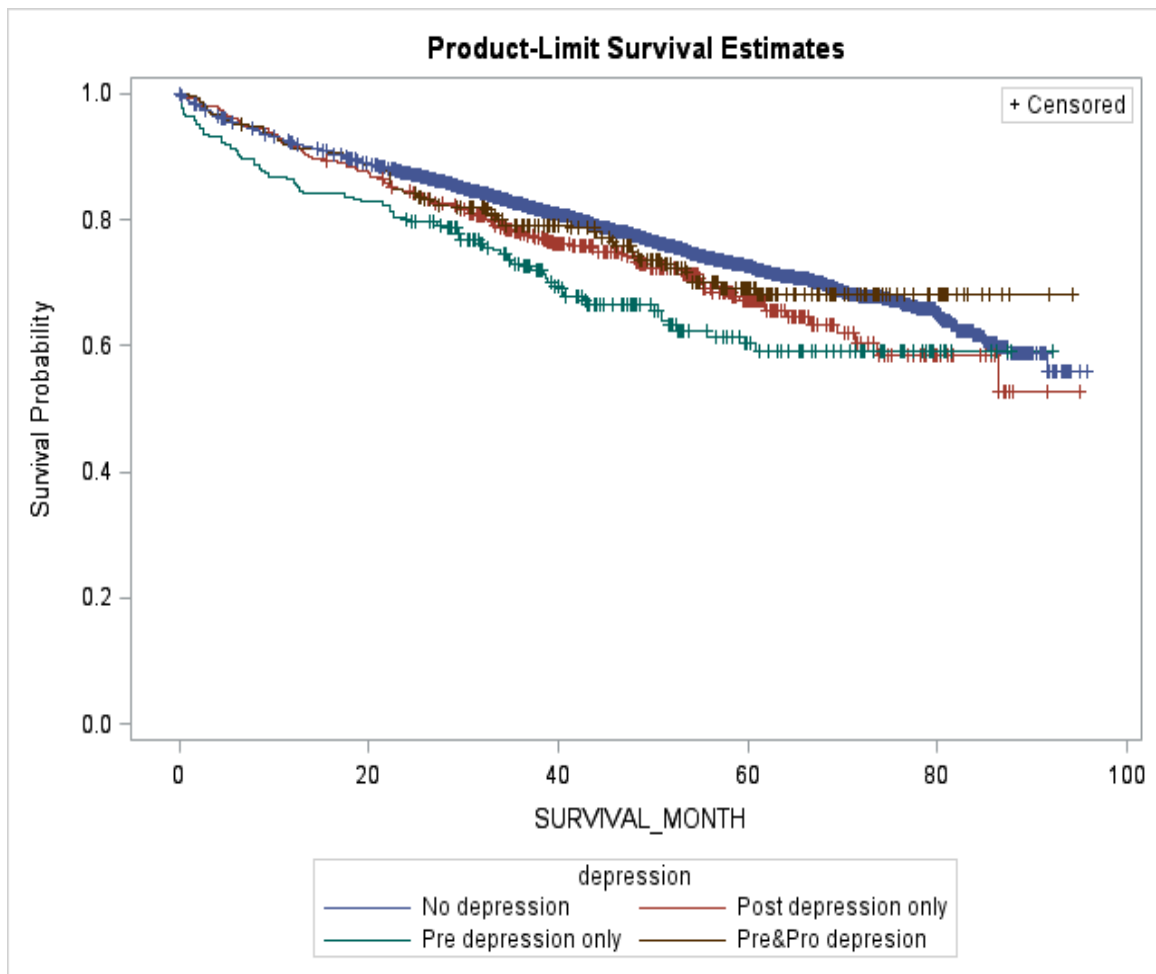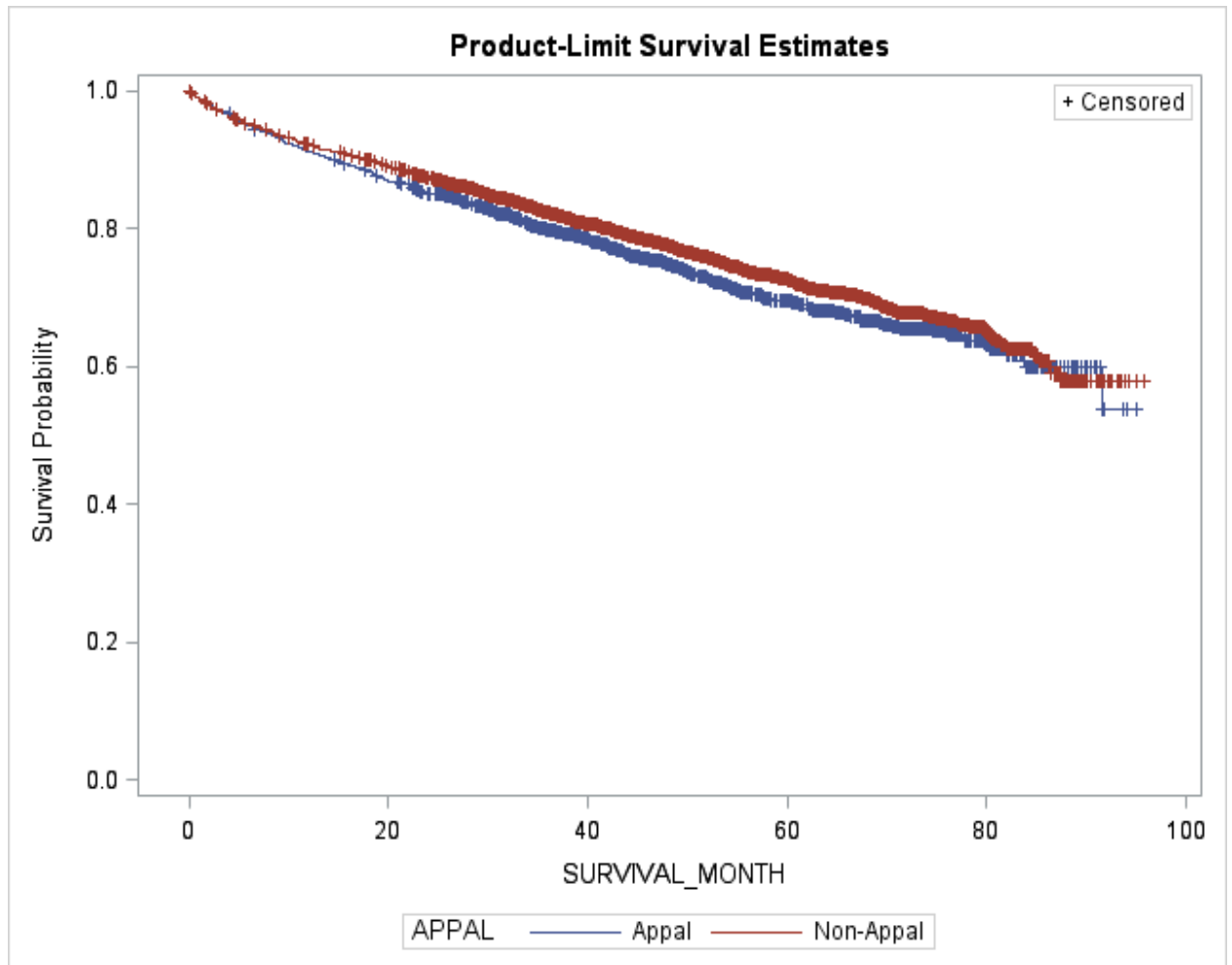
**Figure 2. Survival curves in breast cancer patients grouped based on Appalachian Status**

## Tables 4. Adjusted Cox hazard regression to identify the association between depression and survival.

| Variables | OR | 95% CI | | P-value |
|---|---|---|---|---|
| Depression Status | | | | 0.0003 |
| Pre depression only | 1.23 | 0.97 | 1.56 | |
| Post depression only | 1.50 | 1.23 | 1.82 | |
| Pre & Post depression | 1.16 | 0.90 | 1.49 | |
| No Depression | Ref | | | |
| Applachian Status | | | | 0.0102 |
| Non-Appalachian | 1.20 | 1.04 | 1.37 | |
| Applachian | Ref | | | |
| Age at Diagnosis | | | | <.0001 |
| 50-65 | 1.15 | 0.88 | 1.50 | |
| 65-74 | 1.37 | 1.03 | 1.82 | |
| 75+ | 2.59 | 1.95 | 3.44 | |
| 21-49 | Ref | | | |
| Smoking Status | | | | <.0001 |
| Smoker | 1.38 | 1.23 | 1.55 | |
| Unknown | 1.23 | 1.07 | 1.40 | |
| Non-smoker | | | | |
| Marital Status | | | | <.0001 |
| Never Married | 1.57 | 1.29 | 1.91 | |
| Seperated/Divorced/Widowed | 1.24 | 1.10 | 1.40 | |
| Unknown | 1.10 | 0.85 | 1.43 | |
| Married | | | | |
| High School or more | | | | 0.0008 |
| <65% | 1.38 | 1.15 | 1.65 | |
| 65%-<75% | 1.30 | 1.12 | 1.51 | |
| 75%-<85% | 1.33 | 1.14 | 1.54 | |
| Unknown | 0.79 | 0.32 | 1.93 | |
| >=85% | | | | |
| Primary payer | | | | <.0001 |
| No insurance | 4.53 | 1.42 | 14.49 | |
| Medicare | 1.45 | 1.14 | 1.84 | |
| Medicaid/Other Public | 1.82 | 1.37 | 2.42 | |
| Unknown | 1.81 | 1.35 | 2.43 | |
| Private insurance | Ref | | | |

## Tables 4. Adjusted Cox hazard regression to identify the association between depression and survival (Cont.)

| Variables | OR | 95% CI | | P-value |
|---|---|---|---|---|
| Charlson Score | | | | <.0001 |
| 1 | 1.27 | 1.11 | 1.44 | |
| >=2 | 1.90 | 1.68 | 2.16 | |
| Missing | 1.67 | 1.33 | 2.10 | |
| 0 | | | | |
| Stage | | | | <.0001 |
| Stage II | 1.86 | 1.61 | 2.15 | |
| Stage III | 3.24 | 2.77 | 3.80 | |
| Stage IV | 14.62 | 12.35 | 17.30 | |
| Unknown | 5.16 | 3.80 | 7.01 | |
| Stage I | Ref | | | |
| Hormone Receptor | | | | <.0001 |
| Negative | 1.45 | 1.27 | 1.66 | |
| Unknown | 2.17 | 1.71 | 2.74 | |
| Positive | Ref | | | <.0001 |
| Grade | | | | |
| Moderate | 1.41 | 1.19 | 1.67 | |
| Poorly/Undifferentiate | 1.70 | 1.42 | 2.04 | |
| Unknown | 1.77 | 1.44 | 2.17 | |
| Well | | | | |
| Standard Cancer Treatment | | | | <.0001 |
| No | 2.20 | 1.95 | 2.49 | |
| Unknown | 1.08 | 0.78 | 1.47 | |
| Yes | Ref | | | |

## *RESULTS*

Among the 6054 patients, 5212(86.1%) patients were not diagnosed with depression in both time periods, and 221(3.7%) patients had a depression diagnosis only within one year before the cancer diagnosis; meanwhile, 375(6.2%) patients had new recordings of depression after cancer diagnosis, and 246(4.1%) women both had depression diagnosis before and after cancer diagnosis. Table 1 presents the comparison of demographic characters and clinical information among the four groups. Compared with women who have not been diagnosed with depression, breast cancer patients who were identified as with depression during the baseline and follow-up period were statistically significantly more likely to be smokers, younger, from Medicare/other public insurance, not in a state of marriage, and with more comorbid diseases. Though Appalachian showed a slightly larger percentage of being diagnosed with depression, the increase was not statistically significant (p-value=0.99).

Table 2 displays the results of multivariable logistic regression. In the multivariable logistic regression analysis examining the influence of depression and Appalachian status on receiving nonguideline cancer treatment, 495 patients with unknown treatment information were excluded, and which resulted in 5559 eligible subjects in this analysis. 1770(31.8%) patients were defined as not receiving guideline treatment. After adjusting other variables that might impact the decision of treatment, no statistically significant association was found between depression and receiving nonguideline treatment(p-value=0.282), and patients only had pre-diagnostic depression showed an increased but nonsignificant odds ratio (OR, 1.38; 95% CI, 0.99-1.92) in receiving nonguideline treatment compared to patients without depression. Patients from Appalachian regions showed an increased association with receiving nonguideline treatment (OR, 1.23; 95% CI, 1.02-1.48).

Survival curves obtained from the Kaplan–Meier method (Figure 1) shows that patients diagnosed with depression only within one year before cancer diagnosis had the worst survival (more explanation needed?) Table 3 shows the results from the Cox regression analysis, the adjusted effect of depression on survival among breast cancer patients were shown. The association between depression and mortality was statistically significant(p-value<.001). Patients with new recordings of depression after the cancer diagnosis had a significant risk for death (HR, 1.50; 95% CI, 1.23-1.82). However, increased but nonsignificant risks for death were shown in patients diagnosed with depression only within one year before cancer diagnosis (HR, 1.23; 95% CI, 0.97-1.56) and patients had depression diagnosis in both periods (HR, 1.16; 95% CI, 0.90-1.49). Results also illustrated that patients received nonguideline cancer treatment showed a significantly higher adjusted hazard ratio (HR, 2.20; 95% CI, 1.95-2.49) than those received guideline treatment.

## *LESSONS LEARNED*

- Finish early: This allows ideas and designs to stew. Finishing earlier provides more time to explore details and revise potential errors. Though there's some saying about the power of last-minute adrenalin-panic for increasing productivity, it's much less stressed when projects were planned and conducted ahead.

- Talk about the project. It's important to communicate with others by expressing my own project. In this process, I realized what I knew and didn't know about in this project, then I would search for relative information to learn those points I was not quite understand, and information I was missing helped me stay on track and discover new paths for research. Meanwhile, others may provide precious advice regarding this project.

- Summarize and create a list of resources. At the beginning, I found myself going back again and again to read related papers and study their methods and results, which was time-consuming to search and find those papers. Then, I decided to summarize those papers briefly and put the summary in one single word document. Whenever I needed to get basic information from those papers, I simply used that file to guide me.

- After half of the basic research is done, look for a really good summary of the field to reorient yourself. More broadly, make sure to take a breath and get perspective on your project and goals.

- Most Importantly:
  It is ok to say"I don't know and I am having some troubles". There were times I was having a hard time coding or understanding, but I was afraid to express that and only spent time worrying, which resulted in delays of some tasks. Then I learned the important lesson of admitting "I don't know and I may not on the right track", which actually reflects the sense of responsibility as a member of a team-we should keep on communicating the process of projects and letting others know whether we fully understand what we are doing.

# *FINAL PAPER*

*Tables and Figures were put in the outputs section(page33-41)

**Influence of depression on treatment and survival: a population-based study in patients with breast cancer in Kentucky**

**Abstract**

BACKGROUND

Few prior studies have explored the impact of the combination of depression in two periods (before and after the cancer diagnosis) on guideline cancer treatment and survival among breast cancer survivors. With large area defined as Appalachian regions in Kentucky, the present study also aimed to find the disparity between Appalachian and non-Appalachian regarding developing depression and receiving standard cancer treatment.

METHODS

Kentucky Cancer Registry (KCR) data linked with Medicare, Medicaid, and private insurance claims data was used in this study. 6054 patients with primary invasive breast cancer aged 20 or older at the time of cancer diagnosis from 2007 to 2011 were included. 12 months before and 13 months from cancer diagnosis were two time periods to searching for depression diagnosis in claims data. Multivariate logistic regression and multivariate Cox regression were separately performed to assess the effect of the combination of depression at two periods on patients' receiving of guideline cancer treatment and overall survival.

RESULTS

There was no statistically significant association between depression and receiving nonguideline treatment($p$=0.2815). Patients reside in the Appalachian area had a significantly higher risk of receiving nonguideline cancer treatment (odds ratio, 1.23; 95% CI, 1.02-1.48). Significant associations between depression and survival were found in patients with newly diagnosed depression diagnosis after cancer diagnosis (hazard ratio,1.50; 95% CI, 1.23-1.82). Increased but nonsignificant risks for death were also identified in patients with pre-diagnostic depression only or patients with a depression diagnosis in both periods.

CONCLUSIONS

Depression did not contribute to receiving nonguideline treatment among breast cancer patients, and Appalachian patients were statistically significantly more likely to receive nonguideline treatment. Patients with newly diagnosed depression after the cancer diagnosis had a significantly increased risk of death.

KEYWORDS: depression, breast cancer, guideline cancer treatment, survival, Appalachian

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer except for skin cancer, and it also is  the second leading cause of cancer death in women. Currently, more than three million women are living with breast cancer in the United States[1]. Previous studies have illustrated breast cancer survival is influenced by factors including age, ethnicity, comorbidity, smoking status, socioeconomic factors, stage of cancer at diagnosis, and cancer treatment[2-9].

Depression is a noticeably common mental health outcome among breast cancer survivors, and its hypothesized association with adverse survival in breast cancer patients has been of interest in the past decade. Studies estimated that about 10% to 25% of breast cancer patients experience depression, which is higher compared with matched control group[10,11]; however, associations between depression and survival found by prior studies remained inconsistent. For most studies which determined depression status in breast cancer patients depended on self-report questionnaires, the association between depression and survival has not been recognized[12-16]. Though some of these studies have illustrated the relationship between depression and survival[17-19], the relatively brief depression measurement using questionnaires is limited compared to depression diagnosis based on systematic clinical consultations. By capturing depression based on clinical diagnosis, two large retrospective studies demonstrated breast cancer patients with depression had a higher likelihood of death[20,21]; however, both studies did not include covariates like lifestyle, socioeconomic factors, hormone receptor status. Several of these variables could predict higher mortality in breast cancer patients[8,22-24].

From a clinical perspective, we are also curious about whether patients with a depression diagnosis are a vulnerable patient group that received nonguideline cancer treatment, which also may lead to worse survival in breast cancer survivors. Two previous studies have reported depression as a negative predictor of receiving guideline cancer care[25,26]. However, one study only included elder patients who were 67 years old or older at the time of breast cancer diagnosis[25], and another study conducted in Denmark only assessed the relationship between depression and adjuvant systemic therapy[26].

No prior studies have investigated the influence of combinations of depression in two time periods (before and after cancer diagnosis) on the survival and guideline treatments, which distinguishes breast cancer patients who were not depressed, who were diagnosed with depression only before cancer, who were diagnosed with depression only after cancer diagnosis, and who were depressed before and after cancer diagnosis, and this allows more detailed study on the influence of depression. Previous studies have investigated the effect of pre/post-diagnostic depression on the survival in breast cancer patients[20,21]. One of them explored the influence depending on the onset of depression separately[20], and another only

compared the influence of pre-diagnostic depression and new recordings of depression after cancer daignosis[21].

The Kentucky Cancer Registry (KCR) data linked with Medicare, Medicaid, and private insurance administrative claims data were utilized in this study. Importantly, this study included records from privately insured patients, who continue to comprise the largest segment of US healthcare users, and few population-based studies in this field had been linked to private insurance claims data. Patients resided in Kentucky were obtained from this data. Kentucky has the highest cancer incidence and mortality rates in the U.S. There're 54 counties defined as Appalachian in Kentucky, and many of these counties are identified as economically depressed, the most rural, and underserved communities in the U.S[27]. Cancer death rates in rural Appalachian counties in Kentucky were nearly 36% higher than in non-Appalachian urban areas nationwide. Of note, breast cancers were found at more advanced stages in women living in Appalachian states, and the 3- to 5-year survival rates for all cancers were lower compared with cases from urban non-Appalachian communities[28]. Therefore, except for the primary objectives of examining the influence of depression on standard treatment and survival in breast cancer patients, we also conducted the study with a secondary focus on the Appalachian regions to explore whether there're disparities between Appalachian areas and non-Appalachian areas. In conclusion, we hypothesized that: (1) depression is associated with receiving nonguideline cancer treatment in breast cancer patients; (2) depression predicts worse survival in breast cancer survivors; (3) Appalachian patients are more likely to experience depression and receive nonguideline cancer treatment.

MATERIALS AND METHODS

Data source

Incident breast cancer cases were obtained from the Kentucky Cancer Registry (KCR), which is a member of the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. The KCR data provide information about demographics, tumor characteristics, initial treatment, and survival of cancer patients. In this study, KCR data have been linked to Medicare, Medicaid, and private insurance administrative databases. These administrative databases consist of beneficiaries' covered health care services, from the time of insurance eligibility until dropout o death, which includes inpatient claims, outpatient claims, and prescription drug usage. In addition, to obtain the census tract socioeconomic information, KCR data were linked with the American Community Survey (ACS) 2007-2011 census tract and zip code files by census tract codes. These files were used to derive education level and below poverty percentage.

Study Population

A total of 12792 patients with invasive primary breast cancer and aged 20 or older at the time of cancer diagnosis from 2007 to 2011 were collected from the KCR linked data. Patients diagnosed through autopsy or death certification have already been excluded from this cohort. Subjects who were not continuously enrolled in claims data 12 months before and 13 months from cancer diagnosis were then excluded because of possible incomplete claims for medical services, which yielded 6054 eligible subjects in the study.

Depressions

Depression diagnosis was determined by an algorithm developed by the Centers for Medicare and Medicaid Services (CMS) Chronic Conditions Data Warehouse[29].Individuals were identified with a depression diagnosis if the following International Classification of Diseases, Ninth Revision, Clinical Modification (ICD-9-CM) codes shown in inpatient or outpatient visit in claims data, including : 296.20, 296.21,296.22,296.23,296.24, 296.25,296.26, 296.30, 296.31, 296.32,296.33,296.34, 296.35, 296.36, 298.0, 300.4, 309.0, 309.1, or 311.0.

A baseline period and a follow-up period were used in this cohort study to capture depression diagnosis, and the date of cancer diagnosis was designated as the index date. The period of 12 months prior the cancer diagnosis was defined as the baseline period, and the period included the month of cancer diagnosis and 12 months after the cancer diagnosis was designate as the follow-up period.  Cancer patients were defined as with pre-diagnosis depression if they were with at least one depression diagnosis during the baseline period. Post-diagnosis depression was defined as any depression diagnosis recorded during the follow-up period. According to the depression diagnosis in baseline and follow-up periods, patients were classified as the following four groups: 1. No depression. Patients with no depression diagnosis in both time periods; 2. Pre-diagnostic depression only. Patients only had depression diagnosis in the baseline period and no depression diagnosis in the follow-up period; 3. Post-diagnostic depression only. Patients only had depression diagnosis after cancer diagnosis; 4. Depression in both periods. Patients had depression diagnosis in both baseline and follow-up periods.

Cancer treatment

Standard treatment for breast cancer was based on claims data as therapy received during the follow-up period. Guideline treatment was defined as follows: first all, if patients have hormone receptor-positive (estrogen receptor (ER)-positive or progesterone receptor (PR)-positive) breast cancer, hormone therapy is included as standard care for all stages. Apart from this, for Stage 1 and 2 cancer, modified radical mastectomy or lumpectomy with adjuvant irradiation is required. Meanwhile, if the cancer is not hormone receptor-positive, chemotherapy is defined as standard care. For stages 3, either begin with neoadjuvant therapy or surgery are appropriate, and followed irradiation is required. For stage 4, hormone therapies are used for as long as possible before chemotherapy is introduced if the cancer is hormone receptor-positive. As for patients with hormone-negative cancer, chemotherapy is the primary

treatment. These definitions were based on published practice recommendations[30]. According to these definitions, a new indicator variable was created to imply whether appropriate initial therapy was received for each subject. Because of the incompleteness of immunity therapy for human epidermal growth factor receptor 2(HER2) in KCR linked data, receiving necessary immunity therapy was not defined as a criterion when identifying guideline treatment.

Covariates

Demographic variables included in the analysis such as age at cancer diagnosis, smoking status, race, Appalachian status, marital status, and primary payer were obtained from the KCR data, and they were used to categorize subjects. Age at the cancer diagnosis will be classified into categorical variables. The ACS 2007-2011 census tract and zip code files provided information on the census tract education level and below poverty percentage after being linked with KCR data. Survival after cancer diagnosis in the study population was obtained from KCR. Overall mortality (death from any causes) was of interest in this study, and the censored date is the most recent available date that captures the death information. The Charlson Comorbidity Index developed for claims data was utilized to measure comorbidity. Concerning clinical variables, the stage at cancer diagnosis, grade, tumor size, and estrogen /progesterone receptors status were derived from the KCR data. Cancer treatment information including chemotherapy, radiation therapy, hormone therapy, and surgery was obtained from the claims data.

Statistical Analysis

Patients were classified into four groups based on depression in the baseline and follow-up periods, and the comparison of the characteristics and clinical information among these groups will be conducted. Proportions were used to describe these categorical variables. A chi-square test was used to analyze categorical variables. Multivariable logistic regression will then be performed to examine the adjusted association between depression and receiving nonguideline cancer treatment, as well as the adjusted association between Appalachian status and receiving nonguideline treatment, controlling for age, race, marital status, education level, poverty level, primary payer, stage, comorbidity, hormone receptor status. Patients with unknown treatment information were excluded from this analysis. Survival rates were first illustrated using the Kaplan–Meier method stratified by depression. Multivariate Cox proportional hazards regression was then used to estimate adjusted HR. The Cox regression will be conducted by adjusting age at diagnosis, smoking status, race, marital status, Appalachian status, primary payer, comorbidity, stage, grade, hormone receptor status, her2-neu status, and appropriate cancer treatment. Of note, instead of adjusting treatment types such as surgery, chemotherapy, and radiation therapy, whether receiving guideline cancer care was controlled in this survival analysis. Statistical significances were determined as two-sided P values < .05.

RESULTS

Among the 6054 patients, 5212(86.1%) patients were not diagnosed with depression in both periods, and 221(3.7%) patients had a depression diagnosis only within one year before the cancer diagnosis; meanwhile, 375(6.2%) patients had new recordings of depression after cancer diagnosis, and 246(4.1%) women both had depression diagnosis before and after cancer diagnosis. Table 1 presents the comparison of demographic characters and clinical information among the four groups. Compared with women who have not been diagnosed with depression, breast cancer patients who were identified as with depression during the baseline and follow-up period were statistically significantly more likely to be smokers, younger, from Medicare/other public insurance, not in a state of marriage, and with more comorbid diseases. Though Appalachian showed a slightly larger percentage of being diagnosed with depression, the increase was not statistically significant *(p*-value=0.99).

Table 2 displays the results of multivariable logistic regression. In the multivariable logistic regression analysis examining the influence of depression and Appalachian status on receiving nonguideline cancer treatment, 495 patients with unknown treatment information were excluded, and which resulted in 5559 eligible subjects in this analysis. 1770(31.8%) patients were defined as not receiving guideline treatment. After adjusting other variables that might impact the decision of treatment, no statistically significant association was found between depression and receiving nonguideline treatment($p$-value=0.282), and patients only had pre-diagnostic depression showed an increased but nonsignificant odds ratio (OR, 1.38; 95% CI, 0.99-1.92) in receiving nonguideline treatment compared to patients without depression. Patients from Appalachian regions showed an increased association with receiving nonguideline treatment (OR, 1.23; 95% CI, 1.02-1.48).

Survival curves obtained from the Kaplan–Meier method (Figure 1) shows that patients diagnosed with depression only within one year before cancer diagnosis had the worst survival. Table 3 shows the results from the Cox regression analysis, the adjusted effect of depression on survival among breast cancer patients were shown. The association between depression and mortality was statistically significant(p-value<.001). Patients with new recordings of depression after the cancer diagnosis had a significantly higher risk of death (HR, 1.50; 95% CI, 1.23-1.82). However, increased but nonsignificant risks for death were shown in patients diagnosed with depression only within one year before cancer diagnosis (HR, 1.23; 95% CI, 0.97-1.56) and patients had depression diagnosis in both periods (HR, 1.16; 95% CI, 0.90-1.49). Results also illustrated that patients received nonguideline cancer treatment showed a significantly higher adjusted hazard ratio (HR, 2.20; 95% CI, 1.95-2.49) than those received guideline treatment.

DISCUSSION

In this population-based cohort study in Kentucky, the results can be summarized as follows. We did not find the support for the hypothesis that a diagnosis of depression was associated

with less likelihood of receiving guideline cancer treatment. Newly-diagnosed depression after the cancer diagnosis was identified as a negative predictor of survival for breast cancer patients. Meanwhile, increased but nonsignificant risks for death were shown in patients diagnosed with depression only within one year before cancer diagnosis and patients had depression diagnosis in both periods. As for the discrepancy between Appalachian and non-Appalachian, Appalachian showed increased risks of nonguideline cancer treatment, neither of the two increased risks was statistically significant.

The finding that patients with depression are not a vulnerable group of not receiving guideline cancer treatment was not in accordance with previously studies[25,26]. Compared to Goodwin's focus on a population of patients aged 67 or older[25], our results apply to a broader age range(>=20 years of age). Meanwhile, using diagnostic of depression in this study rather usage of antidepressants[26] as a predictor is more accurate when examining the association between depression and the outcome because anxiety and pain relief constitutes more than one-quarter use of prescribed antidepressants[31,32]. Though, we assumed that patients with depression might show less motivation and a decreased level of self-management, which may lead to a poorer commitment to receiving guideline treatment. Our findings indicated that the adjusted likelihood of receiving nonguideline treatment in patients with depression was not significantly higher than in patients without depression. The discrepancy between receiving guideline treatment or not was more determined by socioeconomic factors and clinical variables such as stage, comorbidity, and hormone receptor status.

A five-year observational cohort study has reported that almost half of the early breast cancer patients expressed depression, anxiety, or both in the first year after cancer diagnosis, and the prevalence dramatically dropped to 25% in the second year[33]. Therefore, the follow-up period of capturing post-diagnosis depression seems feasible in this study. As for pre-diagnosis depression, two other population-based studies of breast cancer mortality have demonstrated significantly worse overall survival in patients with pre-diagnosis depression[20,21]. However, this association was not found in this study; patients who were diagnosed with depression only before cancer diagnosis or had depression both before and after cancer diagnosis did not show significantly worse overall survival compared to patients without depression. This might be explained by the shorter baseline time to capture prior diagnosis of depression in our study compared to two others. One study examined the population of southeast England identified pre-diagnosis depression as any diagnosis of depression three years before cancer breast diagnosis[21]. Another study conducted in Denmark even defined pre-diagnosis depression as any first-ever psychiatric admission with depressive disorders at age 15 years or older before the date of first breast cancer diagnosis[20]. Thus, compared to these two studies, fewer individuals would be determined as with pre-diagnostic depression, and this might result in the different results. Importantly, after removing the variable- "appropriate cancer treatment" from the multivariate Cox regression model, patients with depression diagnosis only before cancer diagnosis showed a significantly worse overall survival (HR=1.41, 95% CI, 1.21-1.74). It implied

that patients in this group are more likely to receive nonguideline treatment, which resulted in worse survival; however, this relationship was adjusted when including the guideline treatment variable in the Multivariate Cox model. Thus, we found a nonsignificant association between pre-diagnostic only and mortality.

Patients with newly diagnosed depression were found significantly more likely to have worse overall survivals. However, there's no significant difference between patients without depression and patients with depression both before and after a cancer diagnosis. This could be interpreted that persistent depression diagnosis represents patients with depression were recognized and managed. Thus, earlier detection and well-management of depression may have had a more positive influence on health behaviors and compliance with cancer treatment. Davis's report also reported a similar conclusion that patients with metastatic breast cancer with decreased depressive symptoms in the first year were more likely to have a longer subsequent survival[34]; thus, we may infer that effective treatment of depression improves survival in patients with breast cancer, though further research is needed to confirm this assumption.

A study has shown that women with depression from poverty regions than all breast cancer had a higher risk of experiencing depression[21]; besides, adjuvant endocrine therapy adherence and persistence was lower in Appalachia regions compared to national level[35]. Therefore, we hypothesized that breast cancer patients residing in Appalachian areas would present higher risks of experiencing depression and receiving nonguideline breast cancer treatment. However, no significant difference of developing depression between Appalachian and non-Appalachian was found in this study. It was likely was due to the lower presence of community mental health clinics, and the lager shortage of mental health-care in Appalachian areas[36], breast cancer patients living in these areas had less access to psychiatry visits and thus were less likely to be diagnosed with depression.

The main advantages of the present study included larger sample size than most of the studies in this field, same classification system, the completeness and sound quality of the KCR registry data and administrative claims data, and the relatively comprehensive controlling for survival-related prognostic covariates. Especially for variables like smoking status, ER status, PR status, and HER2 status, though they are highly associated with breast cancer survival, they were seldom involved in previous studies. Of note, introducing the combination of depression in two periods (before and after the cancer diagnosis) to classify patients could distinguish the effect of thecancer diagnosis on developing depression, which has been seldom used in this field. As for the limitations of this study, first of all, the exclusion of patients without continuous enrollment in claims data may result in the miss of valuable information. It is more often that women with a lower socioeconomic status were more likely to drop from insurance than the general female population[37], and low socioeconomic has consistently shown a relationship with significantly worse survival in breast cancer patients[7].

In conclusion, among women with primary invasive breast cancer in Kentucky, we found that patients from Appalachian had a statistically significantly higher risk for not receiving guideline cancer treatment, and patients only with a pre-diagnostic showed an increase but nonsignificant increased risk of receiving nonguideline treatment. The nonguideline cancer treatment would result in worse survival among these breast cancer patients, which indicates that improvement of breast cancer guideline treatment in this group of patients may increase the post-diagnostic survival in these groups. Besides, newly diagnosed depression after a cancer diagnosis had a significant association with adverse overall mortality. As a result, introducing social support, psychological interventions, or depression screening for breast cancer patients after cancer diagnosis especially within one year after cancer diagnosis were recommended. The target population is patients who are with lower socioeconomic status, living alone, in younger age groups, benefiting from Medicaid or other public insurance, and presenting more comorbidities. As for the different likelihood of receiving nonguideline cancer treatment between Appalachian and non-Appalachian breast cancer patients, improvement of medical services should be promoted for Appalachian patients, which will lead to better survival in this underserved group.

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