INTERACTION OF ALCOHOL CONSUMPTION AND ADJUVANT HORMONE THERAPY IN RELATION TO BREAST CANCER FREE SURVIVAL AMONG WOMEN WITH PRIMARY BREAST CANCER

By

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To Robert Ward

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Alcohol consumption has been consistently associated with an increase in breast cancer risk in previous studies. However, the findings on the associations of alcohol consumption at the time of breast cancer diagnosis with breast cancer-free survival, have been inconsistent. Further, whether the association of alcohol consumption with breast cancer-free survival could differ in women with and without adjuvant hormone therapy is unknown. We examined interactions of alcohol consumption with adjuvant hormone therapy in relation to breast cancer-free survival among women with primary breast cancer diagnosis.

This study utilized data collected by the Moffitt Cancer Center Health and Informatics that links Cancer Registry data with patient reported information. We identified women who were diagnosed with incident breast cancer and treated between 2007-2012, completed the patient survey prior to diagnosis, and had available data on alcohol consumption and important covariates (n=1,399). Alcohol consumption during the 12 months preceding diagnosis was assessed through a self-administered survey and categorized as never, occasional (≤1 drink/month), and current (>1 drink/month) as well as a binary variable (drinker [>1 drinks/month] vs. non-drinker [0 drinks/month]). Information on adjuvant hormone therapy was

available from the treatment data. Cox proportional hazards models were used to describe the association between alcohol consumption and breast cancer-free survival after adjustment for age, body mass index, menopausal status, and relevant treatment.

Overall, alcohol consumption was associated with better breast cancer-free survival (Hazard Ratio [HR]=0.77, 95% CI 0.65-0.92 for any vs. no drinking and HR=0.75, 95% CI 0.62-0.89 for current vs. no drinking). Among women without adjuvant therapy, alcohol consumption was not associated with breast cancer-free survival. Among women with adjuvant therapy, alcohol consumption was associated with better survival (current vs. no drinking: HR=0.68, 95% CI 0.55-0.85 and any vs. no drinking HR=0.71, 95% CI 0.57-0.88). There was no significant interaction between alcohol consumption and adjuvant therapy with either of the exposure modeling approaches (P-interaction>0.05).

Associations of alcohol consumption with breast cancer-free survival are similar in women with and without adjuvant hormone therapy. Future studies are warranted to elucidate potential mechanisms behind the observed inverse associations.

CHAPTER 1
INTRODUCTION

Breast cancer is the most common cancer in women and the second leading cause of cancer mortality in the US and Europe (1, 2). In 2016 in the US, the estimated incidence and mortality of breast cancer were 246,660 and 40,450, respectively (2). Recent advancements in breast cancer treatment have improved patient outcomes and survival (3). The rate of mortality has been falling each year from 2004-2013 in the US for breast cancer (2) indicating the improved effectiveness of treatments.

Breast cancer survival and the risk of recurrence are associated with clinical and morphological tumor characteristics, including stage (which incorporates information on tumor size and nodal involvement), differentiation grade, and receptor status (4, 5). Breast cancer survival worsens and the recurrence risk increases in tumor stages III and IV (6, 7). Survival rates for breast cancer stages are 96%, 85.6%, 59.2% and 25.5% for stage I, II, III, and IV respectively (6) while recurrence rates are 11.5-13.3%, 42.3-48.2%, 60.3-66.1%, 66.7-73.3%, respectively (3). Another study saw a 66% increase in the risk of recurrence per one centimeter increase in tumor size among women (8). Other studies showed that higher tumor grade in women with low tumor size and two positive lymph nodes have a lower 5 and 10-year survival (9) with the 10-year survival for grade 3 being 62% as compared to 86% for grade 1 (6, 9, 10). As with the other clinical tumor factors, studies show that estrogen, progesterone and HER2 receptor status affects survival of breast cancer (10). Survival for women with both estrogen receptor (ER) positive and progesterone receptor (PR) positive tumors is better as compared to ER negative and PR negative tumors (10-12). Across all stages of breast cancer, women with triple negative breast cancer (estrogen receptor negative, progesterone receptor negative, and

HER2 negative) have worse overall and breast cancer cause-specific survival compared to women with non-triple negative breast cancer (13).

In previous studies, breast cancer survival has been associated with some epidemiologic risk factors for breast cancer. Women diagnosed at age younger than 36 years have a higher rate of recurrence and worse 5-year survival compared to women who are older than 36 years at diagnosis (14). Both breast cancer survival and the risk of recurrence have been shown to be positively associated with body mass index (BMI) (15). The risk of breast cancer recurrence in women with BMI>30 is 43% higher than in women with BMI<30 (16).

Alcohol is a well-known breast cancer risk factor with consistent positive associations with breast cancer risk across the studies (17-19). Light alcohol consumption shows a positive association with about a 5% increase in breast cancer risk compared to nondrinkers (17). Moderate alcohol consumption of as little as 5g/day (1/2 drink/day) has a positive association with the risk of breast cancer in African Americans, Japanese Americans, Caucasians, and Latinas (20). High levels of alcohol consumption (>3 drinks/day) increases the risk of breast cancer by 40-50% (17). Alcohol consumption between first menarche and first term pregnancy is also positively associated with an increased risk of breast cancer with hormone receptor positive tumors at exposure level of 10g/day or 6 drinks/week (21). Alcohol intake overall increases the relative risk of breast cancer by 7% for each additional 10g of alcohol per day (22).

Studies on the associations of alcohol and breast cancer outcomes such as recurrence, second primary, and mortality are inconsistent. Some studies have shown no association between recurrence and alcohol consumption while others have found a positive association. Breast cancer recurrence and alcohol consumption did not show a significant association among postmenopausal women but showed a nonlinear negative association with breast cancer mortality

among postmenopausal women (23). One study found that consuming 3-4 drinks/week is associated with an increased risk of recurrence by 50% among postmenopausal women and 60% among obese or overweight women while only postmenopausal women showed a statistically significant increase in risk for breast cancer death post-diagnosis (24). For second primary contralateral breast cancer, a positive association has been seen with alcohol consumption of >7 drinks/week pre-diagnosis with a 70% higher odds compared to nondrinkers (25).

Adjuvant hormone therapy is used after breast cancer diagnosis and surgery to improve overall survival from recurrence and mortality. There is a higher risk of breast cancer recurrence in women that are not adherent to adjuvant hormone therapy (3). Adjuvant hormone therapy has also been shown to improve breast cancer free survival by reducing mortality and the risk of recurrence by 34% and 40%, respectively with a five year treatment (26). In previous studies, tamoxifen improved patient outcomes when taken for five years by reducing the risk of recurrence and mortality; the risk of recurrence also decreased after 10 years of treatment in women with ER positive breast cancer (27). Further, the combination of chemotherapy and tamoxifen may reduce the risk of dying from breast cancer by 50% in women under the age of 50 years and a little less than 50% for women aged 50-69 years (26).

Whether there is an interaction between alcohol consumption and adjuvant hormone therapy is poorly understood. Some previous studies show that concurrent alcohol consumption of >20g/day and postmenopausal hormone therapy increases breast cancer risk by two-fold compared to women without alcohol consumption (28). In this case, there are several biological mechanisms that may explain the potential interaction between alcohol consumption and adjuvant hormone therapy. A plausible biological mechanism is one of the criteria for establishing not just an interaction but a causal relationship according to Sir Bradford Hill. (29).

For example, long-term alcohol consumption may affect the xenobiotic metabolism by altering the metabolism of the drug resulting in higher toxicity and/or dangerous drug interactions (30). Certain drug-metabolizing enzymes such as CYP450, glutathione S-transferases, diphosphate glucuronosyl-transferases are essential for the metabolism of xenobiotics including hormones for adjuvant hormone therapy (31). Long-term alcohol consumption may have potential to influence the activity of these enzymes. CYP19 (aromatase), a crucial enzyme in estrogen metabolism (32), can be induced by alcohol (33), resulting in an altered hormonal environment during adjuvant therapy treatment. The potential interaction between alcohol use and adjuvant therapy has never been investigated. This study aimed to assess the interaction between alcohol consumption and adjuvant hormone therapy in relation to breast cancer-free survival in women with primary breast cancer diagnosis.

CHAPTER 2
METHODS

Study Population

The current study utilizes the cancer registry data collected by the Moffitt Cancer Center (Tampa, FL) which provides cancer care to the population of Hillsborough and Pasco counties in Tampa Bay encompassing a population of nearly 3 million individuals. The Moffitt Cancer Center has collected and stored data on patients diagnosed with any type of cancer and follow up information through the Health and Informatics (HRI) data warehouse. Through agreement collaboration with Dr. Egan, we were provided with de-identified data subset from the HRI for this study. The HRI links data from several clinical systems, a biobank and patient survey upon patient consent. The HRI data warehouse maintains the information on patient's demographics, treatment, survival, tumor-related characteristics, and patient survey data. From HRI data, we identified all women who were diagnosed with incident breast cancer and treated between 2007-2012, completed the patient survey prior to diagnosis, and had available data on alcohol consumption (n=1,407). From these, we excluded eight women missing adjuvant therapy or age at diagnosis. The final study population included 1,399 women. This study was approved by the University of Florida and Moffitt Cancer Center Institutional Review Boards (IRBs).

Assessment of Alcohol Consumption

Alcohol consumption during 12 months preceding diagnosis was assessed through a self-administered patient survey. Participants were asked to report frequency of alcohol consumption, the number of drinks typically consumed and the type of beverage. One drink was defined as one 12 oz. can or bottle of beer, one 5-ounce glass of wine, one can or bottle of a wine cooler, one cocktail or one shot of liquor. Alcohol consumption was categorized as never (0 drinks/month), occasional (≤1 drink/month), and current (>1drinks/month) as well as a binary variable (drinker

[>1 drinks/month] vs non-drinker [0 drinks/month]) (34, 35). Separate analyses were performed using both of these exposure variables.

In a second analysis, alcohol consumption was assessed using frequency of drinks per week. Consumption was categorized as never (0 drinks/week), moderate (≤7drinks/week), and heavy (>7 drinks/week) (36).

Covariates

The survey collected information on potential confounders such as demographics, menopausal status, reproductive history, family history of breast cancer in first degree relatives, types of treatment, and tumor characteristics. Family history was categorized as having no family member with a history of breast cancer or having any first-degree family member with breast cancer (including mother, daughter, sister, father, brother, or son). BMI was calculated using height and weight available from the medical record or reported on the survey. For the majority of the women (n=982), information on BMI was available from within the year preceding the diagnosis. For women with missing BMI from within the year preceding the diagnosis, BMI was retrieved from within two years preceding date of diagnosis (n=27), within the year after diagnosis (n=1), or within two years after diagnosis (n=89). BMI was categorized as underweight/normal (<25kg/m^2), overweight (25-29.9 kg/m^2), obese (>30 kg/m^2), or unknown (n=300).

Outcomes

The history of a secondary malignant breast neoplasm and chemotherapy indicator codes from the cancer registry and patient billing system were used to identify women with the outcomes of interest. This approach was similar to the previously described methods in Hassett et al (37). The primary outcomes of interest included second primary breast cancer, breast cancer recurrence, and death from breast cancer. Second primary breast cancer was defined as having

International Classification of Diseases Identification version 9-Clinical Modification code 198.81 after the primary breast cancer diagnosis. Recurrence was defined as having any of the relevant breast cancer-related treatment that occurred at least 15 months from the date of original diagnosis, in the absence of any new cancer diagnosis for another site. The list of codes for each of the coding system used for recurrence definition is presented in the Appendix. Death from breast cancer was identified through the cancer registry. Women without an outcome of interest were censored at the time of death by other causes or the end of the study (7/31/2015). Out of all women in the study, 559 women had the outcome of interest (85 second primary breast cancers, 439 recurrences, and 35 deaths), and 840 were censored.

Statistical Analysis

Baseline characteristics of women with and without the study outcome were compared with chi-squared (categorical variables) and t-tests (continuous variable) overall and by the status of adjuvant therapy. Fisher's exact test was used for categorical variables when chi-squared was not valid. Cox proportional hazard models were used to calculate hazards ratios (HRs) and corresponding 95% confidence intervals using follow up time as the time variable. Follow up for women with a study outcome was defined by the number of months from the date of diagnosis to the first occurring outcome of interest: breast cancer recurrence, second primary breast cancer, or death from breast cancer. Follow up for women without the outcome was defined as the number of months between primary breast cancer diagnosis and either date of death from other causes or the end of study (7/31/2015), which ever came first. The risk estimates were adjusted for potential confounders and the final model was selected with step wise model selection approach. BMI and age at diagnosis were forced into the final survival model as they have shown associations with breast cancer free survival in previous studies (15, 38). The final survival models included the following covariates: age at diagnosis (years), BMI (normal, overweight,

obese, unknown), immunotherapy (yes, no), hormone therapy (yes, no), surgery (yes, no), chemotherapy (yes, no), and menopausal status (post, other).

The interaction between alcohol consumption (modeled as binary as well as categorical with three levels) and adjuvant therapy (yes, no) was evaluated by including an interaction term in the overall models. Next, the survival analysis was stratified by adjuvant therapy. Proportional hazards assumption was evaluated for each model. Chemotherapy was the only variable to violate the proportional hazards assumptions, in both models. To account for the nonproportionality we added an interaction term with chemotherapy and time (39). All the tests were two-sided and significance of the effects was assessed at 0.05 significance level. All analyses were performed with SAS (SAS Institute Inc. version 9.4).

After looking at our findings, a second analysis was done to determine if the observed associations between alcohol and breast cancer-free survival could be explained by the benefits of moderate drinking. Moderate drinking has been shown to have protective effects on other chronic diseases (40, 41). In this analysis, alcohol consumption was categorized based on the number of drinks per week and the associations were examined overall and by the status of adjuvant therapy. We then conducted additional analysis that excluded women with immunotherapy or chemotherapy to exclude potential masking effects of immune- and chemotherapy on survival. The associations were examined overall and by status of adjuvant therapy. Risk estimates in the models were adjusted for age at diagnosis, BMI, surgery, hormone therapy, adjuvant therapy (except stratified), and menopausal status. The interactions between alcohol consumption and adjuvant therapy were assessed in both secondary analyses. Where needed an interaction term with chemotherapy and time was added to the models to account for nonproportionality.

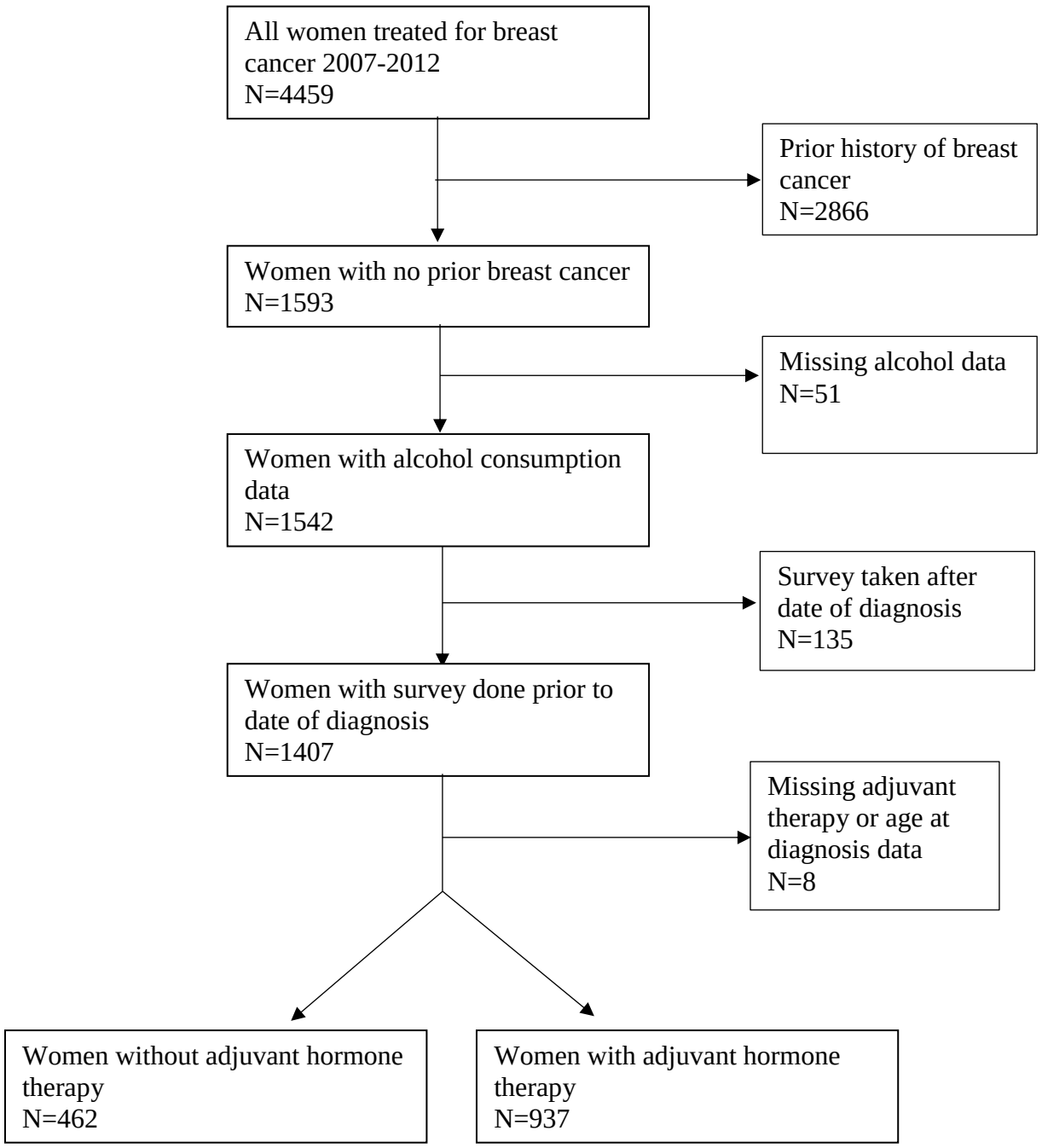

Figure 2-1. Patient selection diagram

CHAPTER 3
RESULTS

This study included 1,399 women with invasive breast cancer (462 women without adjuvant therapy and 937 with adjuvant therapy). Table 3-1 shows characteristics of the study participants by the study outcomes (having breast cancer recurrence, second primary breast cancer, or breast cancer-related death). Women with the outcome were less likely to be drinkers (53.49% vs 59.52%, p=0.0293), more likely to have had chemotherapy (70.84% vs. 42.26%, p<0.0001), more likely to have had immunotherapy (22.36% vs. 8.93%, p<0.0001), and less likely to have had surgery (94.28% vs. 97.98%, p=0.0004) compared to participants without the outcome. Characteristics of patients stratified by adjuvant therapy and outcome are shown in table 3-2. Among women with adjuvant therapy, those with outcome were less likely to be current drinkers (47.57% vs. 55.91%, p=0.0258), less likely to have a progesterone receptor positive tumor (85.95% vs 90.30%, p=0.0335), more likely to have had chemotherapy (71.16% vs. 33.69%, p<0.0001), and more likely to have had immunotherapy (21.35% vs. 6.35%, p<0.0001). Among women without adjuvant therapy, those with the outcome were less likely to have had surgery (83.07% vs. 93.77%, p=0.0004), more likely to have had immunotherapy (24.34% vs. 14.29%, p=0.0088), and more likely to have had hormone therapy (16.93% vs. 5.86%, p=0.0002). Distributions of other characteristics were similar among women with and without the study outcome in both of the adjuvant therapy strata.

Adjuvant therapy was inversely associated with the outcome in the overall model (HR=0.59, 95% CI 0.36-0.95). The results for the association of alcohol consumption with the outcome, overall as well as stratified by adjuvant therapy, are summarized in table 3-3. Overall, alcohol consumption within preceding 12 months was inversely associated with the risk of the study outcomes with a 23% reduction in risk among women with any consumption as compared

to no consumption (HR=0.77, 95% CI 0.65-0.92) and a 25% reduction in risk among current as compared to never drinkers (HR=0.75, 95% CI 0.62-0.89).

Among women without adjuvant therapy, alcohol consumption was not associated with adverse breast cancer-related outcomes after adjustment for the other covariates (occasional vs. no drinking: HR=0.97, 95% CI 0.55-1.70; current vs. no drinking: HR=0.83, 95% CI 0.60-1.13; and any consumption vs. none: HR= 0.85, 95% CI 0.63-1.14).

Among women with adjuvant therapy, alcohol consumption was inversely associated with adverse breast cancer-related outcomes with a 32% reduction in the risk of having the outcome among current as compared to never drinkers (HR=0.68, 95% CI 0.55-0.85) and a 29% reduction in the risk for individuals with any consumption as compared to none (HR=0.71, 95% CI 0.57-0.88).

There was no significant interaction between alcohol consumption and adjuvant therapy with either of the exposure modeling approaches ($p>0.05$ for both).

In secondary analysis among women without immunotherapy or chemotherapy, breast cancer-free survival appeared to be better in women consuming alcohol though these associations no longer reached statistical significance due to a smaller sample size (n=639; current vs. no drinking: HR=0.82, 95% CI 0.57-1.16; any consumption vs. none: HR=0.89, 95% CI 0.64-1.25). Similar, though non-significant results were observed in stratified analyses (among women without adjuvant therapy: current vs. no drinking: HR=1.26, 95% CI 0.67-2.37; any consumption vs. none: HR=1.30, 95% CI 0.70-2.38; and among women with adjuvant therapy: current vs. no drinking: HR=0.70, 95% CI 0.46-1.07; any consumption vs. none: HR=0.78, 95% CI 0.52-1.17). No interaction between alcohol consumption and adjuvant therapy

was found (P-interaction=0.22 and 0.27 for three-level and binary alcohol consumption, respectively).

In the models with alcohol consumption assessed as drinks per week, a better breast cancer-free survival was observed in women consuming alcohol, both overall and by the status of adjuvant therapy (table 3-3). There was no interaction between alcohol consumption and adjuvant therapy (P-interaction=0.42).

Table 3-1. Characteristics of Study Participants by Breast Cancer-Related Outcomes

Characteristic	Without Outcome N=840	With Outcome N=559	P-value
Age at Diagnosis, mean (Standard Deviation)	58.32 (12.28)	56.38 (11.83)	0.3321
BMI n (%)			
Normal	221 (26.31)	122 (21.82)	0.1550
Overweight	208 (24.76)	143 (25.58)	
Obese	213 (25.36)	166 (29.70)	
Unknown	198 (23.57)	128 (22.90)	
Menopausal Status n (%)			
Other	477 (56.79)	300 (53.67)	0.2736
Post	363 (43.21)	259 (46.33)	
Drinking Status n (%)			
Occasional	55 (6.55)	49 (8.77)	0.0079
Never	340 (40.48)	260 (46.51)	
Current	445 (52.98)	250 (44.72)	
Drinker n (%)			
No	340 (40.48)	260 (46.51)	0.0293
Yes	500 (59.52)	299 (53.49)	
Family History n (%)			
Any	148 (17.62)	84 (15.03)	0.2288
None	692 (82.38)	475 (84.97)	
Progesterone Receptor n (%)			
PR-	229 (27.26)	169 (30.18)	0.2649
PR+	596 (70.95)	386 (68.93)	
Borderline	0	1 (0.18)	
Missing	15 (1.79)	4 (0.71)	
Adjuvant therapy n (%)			
Yes	567 (67.50)	370 (66.19)	0.6510
No	273 (32.50)	189 (33.81)	
Chemotherapy n (%)			
No	485 (57.74)	163 (29.16)	<0.0001
Yes	355 (42.26)	396 (70.84)	
Surgery n (%)			
No	17 (2.02)	32 (5.72)	0.0004
Yes	823 (97.98)	527 (94.28)	
Radiation n (%)			
No	332 (39.52)	220 (39.36)	0.9944
Yes	508 (60.48)	339 (60.64)	

Table 3-1. Continued

Characteristic	Without Outcome	With Outcome	P-value
Immunotherapy n (%)			
No	765 (91.07)	434 (77.64)	<0.0001
Yes	75 (8.93)	125 (22.36)	
Hormone Therapy n (%)			
No	263 (31.31)	160 (28.62)	0.3113
Yes	57 (68.69)	399 (71.38)	

Table 3-2. Characteristics of Study Participants by Adjuvant Therapy and Breast Cancer-Related Outcomes

	Without Adjuvant Therapy		P-value	With Adjuvant Therapy		P-value
Characteristic	Without Outcome n=273	With Outcome n=189		Without Outcome n=567	With Outcome n=370	
Age at Diagnosis, mean (Standard Deviation)	58.31 (14.24)	57.65 (12.72)	0.0975	58.32 (11.23)	55.73 (11.31)	0.8869
BMI n (%)						
Normal	82 (30.04)	39 (20.63)	0.1052	139 (24.51)	83 (22.43)	0.4117
Overweight	55 (20.15)	50 (26.46)		153 (26.98)	93 (25.14)	
Obese	64 (23.44)	50 (26.46)		149 (26.28)	116 (31.35)	
Unknown	72 (26.37)	50 (26.46)		126 (22.22)	78 (21.08)	
Menopausal Status n (%)						
Other	142 (52.01)	101 (53.44)	0.8362	335 (59.08)	199 (53.78)	0.1250
Post	131 (47.99)	88 (46.56)		232 (40.92)	171 (46.22)	
Drinking Status n (%)						
Occasional	20 (7.33)	15 (7.94)	0.2534	35 (6.17)	34 (9.16)	0.0258
Never	125 (45.79)	100 (52.91)		215 (37.92)	160 (43.24)	
Current	128 (46.89)	74 (39.15)		317 (55.91)	176 (47.57)	
Drinker n (%)						
No	125 (45.79)	100 (52.91)	0.1582	215 (37.92)	160 (43.24)	0.1193
Yes	148 (54.21)	89 (47.09)		352 (62.08)	210 (56.76)	
Family History n (%)						
Any	45 (16.48)	23 (12.17)	0.2488	103 (18.17)	61 (16.49)	0.5664
None	228 (83.52)	166 (87.83)		464 (81.83)	309 (83.51)	
Progesterone Receptor n (%)						
PR-	175 (64.10)	118 (62.43)	0.4214	54 (9.52)	51 (13.78)	0.0335
PR+	84 (30.77)	68 (35.98)		512 (90.30)	318 (85.95)	
Borderline	0	0		0	1 (0.27)	
Missing	14 (5.13)	3 (1.59)		1 (0.18)	0	

Table 3-2. Continued

Characteristic	Without Adjuvant Therapy		P-value	With Adjuvant Therapy		P-value
	Without Outcome n=273	With Outcome n=189		Without Outcome n=567	With Outcome n=370	
Chemotherapy n (%)						
No	109 (39.93)	60 (31.75)	0.0898	376 (66.31)	103 (27.84)	<0.0001
Yes	164 (60.07)	129 (68.25)		191 (33.69)	267 (71.16)	
Surgery n (%)						
No	17 (6.23)	32 (16.93)	0.0004	0	0	-
Yes	256 (93.77)	157 (83.07)		567 (100)	370 (100)	
Radiation n (%)						
No	128 (46.89)	104 (55.03)	0.1040	204 (36.98)	116 (31.35)	0.1646
Yes	145 (53.11)	85 (44.97)		363 (64.02)	254 (68.65)	
Immunotherapy n (%)						
No	234 (85.71)	143 (75.66)	0.0088	531 (93.65)	291 (78.65)	<0.0001
Yes	39 (14.29)	46 (24.34)		36 (6.35)	79 (21.35)	
Hormone Therapy n (%)						
No	257 (94.14)	157 (83.07)	0.0002	6 (1.06)	3 (0.81)	0.9705
Yes	16 (5.86)	32 (16.93)		561 (98.94)	367 (99.19)	

Table 3-3. Hazard Ratios (HRs) of Second Primary Breast Cancer, Breast Cancer Recurrence, and Death from Breast Cancer by Alcohol Consumption and Adjuvant Therapy

Alcohol consumption	All women		Women without adjuvant therapy		Women with adjuvant therapy	
	N	Hazard Ratio (95% CI) [a]	N	Hazard Ratio (95% CI) [b]	N	Hazard Ratio (95% CI) [b]
Never	442	1.0	156	1.0	286	1.0
Occasional	96	0.96 (0.70,1.30)	34	0.97 (0.55,1.70)	62	0.87 (0.60,1.26)
Current	554	0.75 (0.62,0.89)	155	0.83 (0.60,1.13)	399	0.68 (0.55,0.85)
None	442	1.0	156	1.0	286	1.0
Any	650	0.77 (0.65,0.92)	189	0.85 (0.63,1.14)	461	0.71 (0.57,0.88)
Never	600	1.0	225	1.0	375	1.0
Moderate	224	0.75 (0.58,0.97)	64	0.77 (0.47,1.26)	160	0.69 (0.51,0.94)
Heavy	358	0.72 (0.58,0.89)	113	0.64 (0.43,0.95)	245	0.74 (0.58,0.96)

Abbreviations: CI-confidence interval

[a] Adjusted for age at diagnosis, BMI, surgery, chemotherapy, adjuvant therapy, menopausal status, hormone therapy and immunotherapy.

[b] Adjusted for age at diagnosis, BMI, surgery, chemotherapy, menopausal status, hormone therapy and immunotherapy.

CHAPTER 4
DISCUSSION

Our study, using data from the HRI database, looked at the interaction between prediagnostic alcohol consumption and adjuvant hormone therapy in relation to breast cancer-free survival. Our findings suggest better breast cancer-free survival in women consuming alcohol overall and among women with adjuvant hormone therapy.

Findings on associations of alcohol consumption with breast cancer-free survival from previous studies have been inconsistent (23, 42-44). Kwan et al. reported a 19% increase in risk of breast cancer recurrence in postmenopausal women consuming >3 drinks per week compared to nondrinkers (HR, 1.19, 95% CI, 1.01-1.40) in a cohort of 9,329 women with invasive breast cancer (45). In contrast, Reding et al. saw an inverse association of alcohol consumption in the 5-year period prior to diagnosis with breast cancer mortality among 1,286 women diagnosed before 45 years, with a 30% reduction in risk among drinkers compared to non-drinkers (HR=0.7, 95% CI 0.5-0.9) (46). Several other studies found no associations of alcohol consumption with breast cancer mortality, breast cancer recurrence, or second primary breast cancer (42, 47).

The results from the secondary analysis showed an inverse association of alcohol consumption with the risk of breast cancer-related outcomes in both models. The first model with the exclusion of women with chemotherapy or immunotherapy shows an inverse association of alcohol consumption with adverse breast cancer outcomes even though the association is non-significant. Since our results still show an inverse association, our findings are thus not influenced by potential masking effect of these two treatments. In the other model, among women with drinks per week, there was still an inverse association of alcohol consumption with adverse breast cancer outcomes, overall and stratified by adjuvant therapy. However, there was 217 (27%) women among drinkers in the study that did not have data on the frequency of drinks

per week resulting in a reduced number of women in the analysis. The results from the secondary analysis confirm moderate drinking is not a factor in better survival among drinkers and unknown mechanisms or several mechanisms may be occurring. Also, the results add to the previous research of alcohol consumption and breast cancer survival.

The mechanism for potential effect of alcohol consumption on survival after breast cancer diagnosis from previous studies is unclear but alcohol has been suggested to decrease breast cancer survival through the effects on estrogen metabolism (48). Adjuvant hormone therapy on the other hand, inhibits the action of estrogen on estrogen receptors. Alcohol can induce CYP19 causing an increase in estrogen levels (33). An increase in estrogen levels can result in a change of the hormone environment effecting adjuvant hormone therapy treatment and negatively impacting breast cancer-free survival. On the other hand, alcohol is able to induce enzymes in the P450 family that are involved in the metabolism of tamoxifen and other adjuvant therapy drugs (49). Some primary and secondary metabolites of tamoxifen have better antiestrogenic effects through higher affinity for estrogen receptors compared to tamoxifen such as endoxifen and 4-hydroxytamoxifen (50). The induction of enzymes in the P450 family by alcohol could accelerate the metabolism of tamoxifen resulting in an increase in concentrations of biologically active metabolites that inhibit action of estrogen on estrogen receptors potentially leading to better survival (51). The final net effect of the alcohol on breast cancer-free survival would depend on relative contribution of these two potential mechanisms working in opposite directions. Our results suggest that better survival among drinkers could potentially be driven by the activation of CYP450 family rather than the effect of alcohol on CYP19.

One of the strengths of our study is utilizing hospital-based cancer registry data with detailed information on tumor characteristics and treatment, and linkage with patient-reported

information. However, our study had a few limitations. Information for demographics and alcohol consumption was self-reported. Previous studies have shown high accuracy in recall of self-reported alcohol consumption in men and women (52-54). However, misclassification of alcohol cannot be completely ruled out as it is always a concern when using a self-reported questionnaire. Another limitation is the inability to assess alcohol consumption as drinks per week as we only had drinks per month for all patients. For drinks per week, 73% of drinkers did not have data.

In addition to the ICD-9 codes, our study used patient's billing system to determine second primary breast cancer and breast cancer recurrence. Even though this method demonstrated high validity in the previous studies, some misclassification of the breast cancer outcomes cannot be ruled out completely. Hassett et al. reported a specificity of 99% for using billing codes to define breast cancer recurrence. In a cohort of 2,726 women with breast cancer, the sensitivity for using billing codes for outcome definition was 79-81% for either breast cancer recurrence or second primary breast cancer (37).

Our findings show a similar association of alcohol consumption with breast cancer-free survival among women with and without adjuvant hormone therapy. Also, our results suggest an inverse association of alcohol consumption with breast cancer-free survival among women with adjuvant hormone therapy. Future studies are needed to determine the interaction between alcohol consumption and adjuvant hormone therapy in relation to breast cancer-free survival and elucidate potential mechanisms behind the observed associations.

APPENDIX
SECOND PRIMARY BREAST CANCER AND CHEMOTHERAPY CODES

Table A-1. Second Primary Breast Cancer and Chemotherapy Codes

Secondary Malignant Neoplasm	
	ICD 9
198.81	Second malig neo breast
Chemotherapy	
	ICD 9
00.10	Implantation of chemotherapy agent
17.70	intravenous infusion of clofarabine (17.70)
99.25	Injection or infusion of cancer chemotherapeutic substance
99.28	Injection or infusion of biological response modifier ÝBRM¨ as an antineoplastic agent
99.29	Injection or infusion of other therapeutic or prophylactic substance
v58.1	Encounter for chemotherapy and immunotherapy for neoplastic conditions
v58.11	Encounter for antineoplastic chemotherapy
v58.12	Encounter for antineoplastic immunotherapy
v66.2	Convalescence and palliative care - Following chemotherapy
v67.2	Follow-up examination - Following chemotherapy
e930.7	Antineoplastic antibiotics (daunorubicin, mitomycin, etc.)
e933.1	Primarily systemic agents - Antineoplastics and immunosuppresive drugs
	Diagnosis-related Groups
410	Chemotherapy w/o acute leukemia as secondary diagnosis
492	Chemotherapy w acute leukemia as secondary diagnosis
	Revenue Center
0331	Radiology therapeutic - chemotherapy injected
0332	Radiology therapeutic - chemotherapy oral
0335	Radiology therapeutic - chemotherapy IV
	Berenson-Eggers Type of Service
O1D	Chemotherapy
	Current Procedure Terminology
36260	Insertion of implantable intra-arterial infusion pump
36640	Arterial catheterization for prolonged infusion therapy (chemotherapy),
36823	Insertion of arterial and venous cannula(s) for isolated extracorporeal circulation
61215	Insertion of subcutaneous reservoir, pump or continuous infusion system
61517	Implantation of brain intracavitary chemotherapy agent
62360	Implantation or replacement of device for intrathecal or epidural drug infusion;

Table A-1. Continued

	Current Procedure Terminology
62361	Implantation or replacement of device for intrathecal or epidural drug infusion;
62362	Implantation or replacement of device for intrathecal or epidural drug infusion;
62365	Removal of subcutaneous reservoir or pump, previously implanted for intrathecal…
90765	Intravenous infusion, for therapy, prophylaxis, or diagnosis
90766	Intravenous infusion, for therapy, prophylaxis, or diagnosis
90767	Intravenous infusion, for therapy, prophylaxis, or diagnosis
90768	Intravenous infusion, for therapy, prophylaxis, or diagnosis
90772	Therapeutic, prophylactic or diagnostic injection
90773	Therapeutic, prophylactic or diagnostic injection
90774	Therapeutic, prophylactic or diagnostic injection
90775	Therapeutic, prophylactic or diagnostic injection
90776	Therapeutic, prophylactic or diagnostic injection
90779	Unlisted therapeutic, prophylactic or diagnostic intravenous or intra-arterial
90780	IV INFUSION THERAPY/DX, GIVEN BY/UNDER DIRECTION, PHYSICIAN: UP TO 1 HR
90781	IV INFUSION THERAPY/DX, GIVEN BY/UNDER DIRECTION, PHYSICIAN: EACH ADDL HR
90782	THERAPEUTIC/PROPHYLACTIC/DX INJECTION (SPECIFY MATL INJECTED): SUBQ/IM
90783	THERAPEUTIC/PROPHYLACTIC/DX INJECTION (SPECIFY MATL INJECTED): INTRA-ARTERIAL
90784	THERAPEUTIC/PROPHYLACTIC/DX INJECTION (SPECIFY MATL INJECTED): IV
90799	UNLISTED PROC, INJECTION, THERAPEUTIC/PROPHYLACTIC/DX
95990	Refilling and maintenance of implantable pump or reservoir for drug delivery
95991	Refilling and maintenance of implantable pump or reservoir for drug delivery
96365	Intravenous infusion, for therapy, prophylaxis, or diagnosis
96366	Intravenous infusion, for therapy, prophylaxis, or diagnosis
96367	Intravenous infusion, for therapy, prophylaxis, or diagnosis
96368	Intravenous infusion, for therapy, prophylaxis, or diagnosis
96379	Unlisted therapeutic, prophylactic, or diagnostic intravenous or intra-arterial
96400	CHEMOTHERAPY ADMINISTRATION, SUBQ/IM, W/WO LOCAL ANESTHESIA
96401	Chemotherapy administration, subcutaneous or intramuscular non-hormonal anti-neoplastic
96402	Chemotherapy administration, subcutaneous or intramuscular hormonal anti-neoplastic
96405	Chemotherapy administration: intralesional, up to and including 7 lesions
96406	Chemotherapy administration: intralesional, more than 7 lesions
96408	CHEMOTHERAPY ADMINISTRATION, IV: PUSH TECHNIQUE
96409	Chemotherapy administration: intravenous, push technique, single or initial substance
96410	CHEMOTHERAPY ADMINISTRATION, IV: INFUSION, UP TO 1 HR

Table A-1. Continued

	Current Procedure Terminology
96411	Chemotherapy administration: intravenous, push technique, each additional substance
96412	CHEMOTHERAPY, IV: INFUSION, 1-8 HR, ADDL HR
96413	Chemotherapy administration, intravenous infusion technique: up to 1 hour, single
96413	Chemotherapy administration, intravenous infusion technique: up to 1 hour, single
96414	CHEMOTHERAPY, IV: INFUSION, > 8 HR W/PORTABLE/IMPLANTABLE PUMP
96415	Chemotherapy administration, intravenous infusion technique: each additional hour
96416	Chemotherapy administration, intravenous infusion technique: initiation of prolonged
96417	Chemotherapy administration, intravenous infusion technique: each additional
96420	Chemotherapy administration, intra-arterial: push technique
96422	Chemotherapy administration, intra-arterial: infusion technique, up to one hour
96423	Chemotherapy administration, intra-arterial: infusion technique, each additional
96425	Chemotherapy administration, intra-arterial: infusion technique
96440	Chemotherapy administration into pleural cavity
96445	Chemotherapy administration into peritoneal cavity
96446	Chemotherapy administration into peritoneal cavity via indwelling port or catheter
96450	Chemotherapy administration, into CNS (eg, intrathecal)
96520	REFILLING & MAINTENANCE, PORTABLE PUMP
96521	Refilling and maintenance of portable pump
96522	Refilling and maintenance of implantable pump or reservoir for drug delivery
96523	Irrigation of implanted venous access device for drug delivery systems
96530	REFILLING & MAINTENANCE, IMPLANTABLE PUMP/RESERVOIR DRUG DELIVERY, SYSTEMIC
96542	Chemotherapy injection, subarachnoid or intraventricular via subcutaneous reservoir
96545	PROVISION, CHEMOTHERAPY AGENT
96549	Unlisted chemotherapy procedure
96567	Photodynamic therapy by external application of light to destroy premalignant and/or malignant lesions
96570	Photodynamic therapy by endoscopic application of light to ablate abnormal tissue
96571	Photodynamic therapy by endoscopic application of light to ablate abnormal tissue
96910	Photochemotherapy; tar and ultraviolet B (Goeckerman treatment) or petrolatum and ultraviolet B
96912	Photochemotherapy; psoralens and ultraviolet A (PUVA)
99601	Home infusion/specialty drug administration, per visit (up to 2 hours):
99602	Home infusion/specialty drug administration, per visit (up to 2 hours): each additional
0169T	Stereotactic placement of infusion catheter(s) in the brain for delivery of therapy
0519F	Planned chemotherapy regimen, including at a minimum: drug(s) prescribed, dose,
4180F	Adjuvant chemotherapy referred, prescribed, or previously received for Stage III

Table A-1. Continued

	Healthcare Common Procedure Coding System
C1084	Denileukin diftitox, 300 mcg
C1086	Temozolomide, 5 mg
C1166	INJECTION, CYTARABINE LIPOSOME, PER 10 MG
C1167	INJECTION, EPIRUBICIN HYDROCHLORIDE, 2 MG
C1178	INJECTION BUSULFAN PER 6 MG
C8953	CHEMOTHERAPY ADMIN IV, PU
C8954	CHEMO ADMIN IV, INFUS UP
C8955	CHEMO ADMN IV, INFUS EA A
C9004	Gemtuzumab ozogamicin inj,5m
C9012	Injection, arsenic trioxide
C9110	INJECTION, ALEMTUZUMAB, PER 10 MG/ ML
C9205	INJECTION, OXALIPLATIN, PER 5 MG
C9207	INJECTION, BORTEZOMIB, PER 3.5 MG
C9213	INJECTION, PEMETREXED, PER 10 MG
C9214	INJECTION, BEVACIZUMAB, PER 10 MG
C9215	INJECTION, CETUXIMAB, PER 10 MG
C9216	INJECTION, ABARELIX FOR INJECTABLE SUSPENSION, PER 10 MG
C9235	Injection, panitumumab, 10 mg
C9257	Injection, bevacizumab, 0.25 mg
C9262	Fludarabine phosphate, oral, 1 mg
C9414	ETOPOSIDE, ORAL, BRAND NAME, 50 MG
C9415	DOXORUBICIN HCL, BRAND NAME, 10 MG
C9417	BLEOMYCIN SULFATE, BRAND NAME, 15 UNITS
C9418	CISPLATIN, POWDER OR S0LUTION, BRAND NAME, PER 10 MG
C9419	INJECTION, CLADRIBINE, BRAND NAME, PER 1 MG
C9420	CYCLOPHOSPHAMIDE, BRAND NAME, 100 MG
C9421	CYCLOPHOSPHAMIDE, LYOPHILIZED, BRAND NAME, 100 MG
C9422	CYTARABINE, BRAND NAME, 100 MG
C9423	DACARBAZINE, BRAND NAME, 100 MG
C9424	DAUNORUBICIN, BRAND NAME, 10 MG
C9425	ETOPOSIDE, BRAND NAME, 10 MG
C9426	FLOXURIDINE, BRAND NAME, 500 MG
C9427	IFOSFAMIDE, BRAND NAME, 1 GM
C9429	IDARUBICIN HYDROCHLORIDE, BRAND NAME, 5 MG
C9431	PACLITAXEL, BRAND NAME, 30 MG
C9432	MITOMYCIN, BRAND NAME, 5 MG
C9433	THIOTEPA, BRAND NAME, 15 MG
C9434	Gallium ga 67, brand
C9436	AZATHIOPRINE, PARENTERAL, BRAND NAME, PER 100 MG
C9437	CARMUSTINE, BRAND NAME, 100 MG
C9438	CYCLOSPORINE, ORAL, BRAND NAME, 100 MG
C9440	VINORELBINE TARTRATE, BRAND NAME, PER 10 MG
G0355	CHEMO SQ/IM NONHORMONL AN

Table A-1. Continued

	Healthcare Common Procedure Coding System
G0357	CHEMOTHERAPY IV PUSH, SINGLE/INITIAL DRUG
G0358	CHEMOTHERAPY ADMINSTRATION OF EACH ADD. PUSHED CHEMO DRUG
G0359	CHEMO IV INFUS,UP TO 1 HR
G0360	CHEMO ADMIN IV INFUS, EA
G0361	INIT PROLNG CHEMO INFUS R
G0362	CHEMOTHERAPY ADMINSTRATION OF EACH INFUSED CHEMO DRUG, UP TO 1 HR
G8372	CHEMO DOC RECV STAGE III
G8373	CHEMO PLAN DOC PRIOR CHEM
G8374	CHEMO PLAN NOT DOC PRIOR
G9021	CHEMO ASSESS NV LEVL 1: N
G9022	CHEMO ASSESS NV LEVL 2: L
G9023	CHEMO ASSESS NV LEVL 3: Q
G9024	CHEMO ASSESS NV LEVL 4: V
G9025	CHEMO ASSESS PAIN LVL 1:
G9026	CHEMO ASSESS PAIN LVL 2:
G9027	CHEMO ASSESS PAIN LVL 3:
G9028	CHEMO ASSESS PAIN LVL 4:
G9029	CHEMO ASSESS FATIGUE 1: N
G9030	CHEMO ASSESS FATIGUE LVL
G9031	CHEMO ASSESS FATIGUE 3: Q
G9032	CHEMO ASSESS FATIGUE LVL
J0207	INJECTION, AMIFOSTINE, 500 MG
J0594	Injection, busulfan, 1 mg
J0640	INJECTION, LEUCOVORIN CALCIUM, PER 50 MG
J0641	INJECTION, LEVOLEUCOVORIN CALCIUM, 0.5 MG
J0894	INJECTION, DECITABINE, 1 MG
J1190	INJECTION, DEXRAZOXANE HYDROCHLORIDE, PER 250 MG
J7150	Prescription Oral Chemo Drug
J8510	Busulfan: oral, 2 mg
J8520	Capecitabine, oral, 150 mg
J8521	Capecitabine, oral, 500 mg
J8530	Cyclophosphamide: oral, 25 mg
J8560	Etoposide; oral, 50 mg
J8565	Gefitinib, oral, 250 mg
J8600	Melphalan: oral, 2 mg
J8610	Methotrexate: oral, 2.5 mg
J8700	Temozolomide, oral, 5 mg
J8705	TOPOTECAN, ORAL, 0.25 MG
J8999	Prescription drug, oral, chemotherapeutic, NOS
J9000	Doxorubicin HCl, 10 mg
J9001	Doxorubicin HCl, all lipid formulations, 10 mg

Table A-1. Continued

	Healthcare Common Procedure Coding System
J9010	Alemtuzumab, 10 mg
J9015	Aldesleukin, per single use vial
J9017	Arsenic trioxide, 1 mg
J9020	Asparaginase, 10,000 units
J9025	Injection, azacitidine, 1 mg
J9027	Injection, clofarabine, 1 mg
J9033	INJECTION, BENDAMUSTINE HCL, 1 MG
J9035	Injection, bevacizumab, 10 mg
J9040	Bleomycin sulfate, 15 units
J9041	Injection, bortezomib, 0.1 mg
J9045	Carboplatin, 50 mg
J9050	Carmustine, 100 mg
J9055	Injection, cetuximab, 10 mg
J9060	Cisplatin, powder or solution, per 10 mg
J9062	Cisplatin, 50 mg
J9065	Injection, cladribine, per 1 mg
J9070	Cyclophosphamide, 100 mg
J9080	Cyclophosphamide, 200 mg
J9090	Cyclophosphamide, 500 mg
J9091	Cyclophosphamide, 1 g
J9092	Cyclophosphamide, 2 g
J9093	Cyclophosphamide, lyophilized, 100 mg
J9094	Cyclophosphamide, lyophilized, 200 mg
J9095	Cyclophosphamide, lyophilized, 500 mg
J9096	Cyclophosphamide, lyophilized, 1 g
J9097	Cyclophosphamide, lyophilized, 2 g
J9098	Cytarabine liposome, 10 mg
J9100	Cytarabine, 100 mg
J9110	Cytarabine, 500 mg
J9120	Dactinomycin, 0.5 mg
J9130	Dacarbazine, 100 mg
J9140	Dacarbazine, 200 mg
J9150	Daunorubicin, 10 mg
J9151	Daunorubicin citrate, liposomal formulation, 10 mg
J9160	Denileukin diftitox, 300 mcg
J9170	Docetaxel, 20 mg
J9171	Injection, docetaxel, 1 mg
J9178	Injection, epirubicin HCl, 2 mg
J9180	EPIRUBICIN HYDROCHLORIDE, 50 MG
J9181	Etoposide, 10 mg
J9182	Etoposide, 100 mg
J9185	Fludarabine phosphate, 50 mg
J9190	Fluorouracil, 500 mg

Table A-1. Continued

	Healthcare Common Procedure Coding System
J9200	Floxuridine, 500 mg
J9201	Gemcitabine HCl, 200 mg
J9206	Irinotecan, 20 mg
J9207	INJECTION, IXABEPILONE, 1 MG
J9208	Ifosfamide, per 1 g
J9209	Mesna, 200 mg
J9211	Idarubicin HCl, 5 mg
J9230	Mechlorethamine HCl, (nitrogen mustard), 10 mg
J9245	Injection, melphalan HCl, 50 mg
J9250	Methotrexate sodium, 5 mg
J9260	Methotrexate sodium, 50 mg
J9261	Injection, nelarabine, 50 mg
J9263	Injection, oxaliplatin, 0.5 mg
J9264	Injection, paclitaxel protein-bound particles, 1 mg
J9265	Paclitaxel, 30 mg
J9266	Pegaspargase, per single dose vial
J9268	Pentostatin, per 10 mg
J9270	Plicamycin, 2.5 mg
J9280	Mitomycin, 5 mg
J9290	Mitomycin, 20 mg
J9291	Mitomycin, 40 mg
J9293	Injection, mitoxantrone HCl, per 5 mg
J9300	Gemtuzumab ozogamicin, 5 mg
J9302	Injection, ofatumumab, 10 mg
J9303	Injection, panitumumab, 10 mg
J9305	Injection, pemetrexed, 10 mg
J9310	Rituximab, 100 mg
J9320	Streptozocin, 1 g
J9330	INJECTION, TEMSIROLIMUS, 1 MG
J9340	Thiotepa, 15 mg
J9350	Topotecan, 4 mg
J9355	Trastuzumab, 10 mg
J9357	Valrubicin, intravesical, 200 mg
J9360	Vinblastine sulfate, 1 mg
J9370	Vincristine sulfate, 1 mg
J9375	Vincristine sulfate, 2 mg
J9380	Vincristine sulfate, 5 mg
J9390	Vinorelbine tartrate, per 10 mg
J9600	Injection, porfimer sodium, 75 mg
J9999	NOC, antineoplastic drug
Q0083	Chemotherapy administration by other than infusion technique only
Q0084	Chemotherapy administration by infusion technique only, per visit
Q0085	Chemotherapy administration by both infusion technique and other technique(s)

Table A-1. Continued

	Healthcare Common Procedure Coding System
Q2017	INJECTION, TENIPOSIDE, 50 MG
Q2024	Injection, bevacizumab, 0.25 mg
S0087	Alemtuzumab injection, 30 mg
S0088	Imatinib injection, 100 mg
S0115	BORTEZOMIB, 3.5 MG
S0116	BEVACIZUMAB 100 MG
S0172	CHLORAMBUCIL, ORAL, 2MG
S0176	HYDROXYUREA, ORAL, 500MG
S0178	LOMUSTINE, ORAL, 10MG
S0182	PROCARBAZINE HYDROCHLORIDE, ORAL, 50MG
S5019	Chemotherapy admin supplies
S5020	Chemotherapy admin supplies
S9329	Home infusion therapy, chemotherapy infusion: administrative services
S9330	Home infusion therapy, continuous (24 hours or more) chemotherapy infusion:
S9331	Home infusion therapy, intermittent (less than 24 hours) chemotherapy infusion:

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BIOLOGICAL SKETCH

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