Differential Patterns of Second Primary Cancers in Whites and Blacks

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Dedication

I dedicate this dissertation to the love of my life and husband Baker Maktabi for believing in me and for giving me someone to look up to, to my Mia for bestowing upon me the highest honor of being her mother and for allowing me a taste of selfless unconditional love, to Dr Donald E. Henson for being my academic father and helping me stay the course. Above all, I dedicate this dissertation to every cancer patient with the hope that a definitive cure is not far away.

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Abstract

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OBJECTIVE

In this dissertation, we examined the incidence and clinical presentation of select second primary cancers following a first primary breast or colorectal cancer (CRC) among Blacks and Whites in the United States. We first quantified the incidence of hormonally-related second primary breast, endometrial and ovarian cancers following a first primary cancer of the breast in Black and White women. Then we compared the patho-epidemiological patterns of second primary contralateral breast cancers in Black and White women to those of the first primary tumors. Finally, we explored the incidence of second primary CRC in Black and White female and male survivors of a first primary colorectal cancer.

METHODS

The National Cancer Institute's Surveillance, Epidemiology, and End Results Registry 9 database was used to follow 450,936 breast cancer survivors, and 299,096 colorectal cancer survivors, diagnosed at age 19 or older, for the occurrence of select second primary cancers between 1973 and 2007. The Van Der Waerden test was used to compare the distributions of continuous clinical characteristics of the first primary and second primary cancers, between Black and White women. The paired T-test or its non-parametric equivalent, the Wilcoxon signed-rank test, was used to compare the distributions of paired continuous variables between the first primary and the second primary cancers, within White and within Black women separately. McNemar's test was used to examine the association of the first primary and second primary cancers with respect to a paired

categorical variable with two levels, within Whites and within Blacks separately; Bhapkar's test was used instead when the variable had more than two levels. The standardized incidence Ratio was used to quantify the risk of events in comparison to the US general population. Cumulative incidence curves, which account for competing events such as death, were generated to describe, among first primary cancer survivors, the probability of developing a second primary cancer. Pepe and Mori's test, which is a two-sample test of the equality of two cumulative incidence functions, was used to test for significant differences in cumulative incidence of second cancers by race.

RESULTS

Results indicated that the incidence of second primary breast cancer was higher among Blacks, and that the incidence of second primary endometrial and ovarian cancers was higher among Whites, independent of the age at diagnosis of the first primary breast cancer. Further examination showed that second contralateral breast cancers presented at an earlier age in Black women, and were more likely to be larger, less differentiated, and had a comparable numbers of lymph nodes as Whites. Also, second contralateral breast cancers were more likely to have a concordant histology and a congruent estrogen receptor status as the first primary breast cancer. As for CRC, the incidence of second primary colorectal cancer increased with age and was significantly higher in men than in women only among patients diagnosed with a first primary CRC > 50. There was no significant difference in the cumulative incidence of second primary CRC between Blacks and Whites.

CONCLUSIONS

Our results contribute to the scarce literature on second primary cancer incidence in Blacks and Whites. In contrast to the Black-to-White crossover of first primary breast cancer around age 45, the incidence of hormonally related second primaries does not appear affected by the age at diagnosis of the first primary. Furthermore, the concordance in clinical presentation between the first primary and second contralateral breast cancers provides preliminary support for the possible bilaterality of many cases of breast cancer, and to a shared etiology between cancers in the two contralateral breasts. The increase in incidence of second primary CRC with age lends further support to the theory of a linear age-specific long-term multistep adenoma-to-carcinoma sequence. The higher incidence of second primary CRC rates in men after age 50 appear to be a function of genetic factors and hormone supplementation. The effect of calendar year on the rates of first primary CRC starting in the mid-1980s, but not second primary CRC incidence rates, suggests that it is unlikely that the differences in CRC incidence between Blacks and Whites would have a purely biological basis.

PUBLIC HEALTH SIGNIFICANCE

This dissertation has established a successful framework for the study of second primary cancer incidence. Our results contribute to the understanding of cancer disparities between Blacks and Whites by comparing incidence patterns of first and second primary cancers. Our results also expand the current understanding of cancer pathogenesis by comparing the clinical parameters of second primary cancers between Blacks and Whites to those of the first primary cancer.

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Chapter 1: Introduction

Previously a fatal disease, cancer has been transformed over the past three decades into a potentially curable condition. A longer life expectancy, an aging population, effective screening and prevention, in addition to improvements in cancer treatment, has led to a burgeoning population of cancer survivors. Since 1971, the number of cancer survivors has tripled, totaling 10.7 million in 2004, and growing at an annual rate of 2%.[1,2] The 5-year relative survival for all cancers combined increased progressively, from 50% in 1975-1979 to 66% in 1996-2002 among adults in the U.S.[3]

However, patients who survive a first primary cancer are not immune from a second primary cancer. In fact, cancer survivors have a 14 percent higher risk of developing a second primary malignancy than individuals have in developing a first primary cancer.[4] In 2004, subsequent malignancies among cancer survivors comprised 16% of the total incident cancer cases reported to the National Cancer Institute's (NCI) Surveillance, Epidemiology, and End Results Program (SEER).[5]

Definition of a Second Primary Cancer

According to the definition adopted by SEER, a second primary cancer is one that arises independently in a new anatomic site or tissue at least two months subsequent to the diagnosis of the first primary cancer, or arises in the same primary anatomic site but has a different histopathology from the first primary cancer. It is distinguished from a "metastatic" cancer, in

which the primary cancer has spread to a new site from the site in which it first appeared. It is also distinguished from a "recurrence" which shares the same histopathology and arises in the same anatomic site less than two months following the diagnosis of the first primary cancer. Exceptions exist for some recurrent cancers and cancers of the same histology reported within two months such as retinoblastoma, bilateral ovarian cancers, adenocarcinomas of the prostate, certain bladder cancers, and several others.

Second primary cancers are described as "synchronous" if they arise within two months following the first primary; they are described as "metachronous" if they arise more than two months following the first primary. As such, second primary cancers are usually metachronous. Therefore, multiple second primary cancers refer to different neoplasms that are diagnosed simultaneously more than two months following the first primary cancer. When both sides of a paired organ are involved with the same histologic type within two months of the initial diagnosis, they are considered multiple primaries only in cases when the physician states them independent primaries or when there is no physician statement that one is metastatic from the other; they are otherwise considered a single second primary cancer. [6] It is important to note that other entities such as the International Association for Cancer Registries (IACR) follow different coding rules for multiple primary cancers. For instance, the IACR does not take into account the lapse between cancer diagnoses and considers all cancers occurring in bilateral organs as one primary.[7]

Differences between Blacks and Whites

Despite the recent decline in cancer incidence and mortality, Blacks continue to suffer higher rates than Whites for most anatomic sites.[8,9] Among men and women of all race/ethnicities, Black men had the highest incidence rate for all cancer sites combined during 2002-2006.[8] Black men and women also had the highest mortality rates of all cancers combined during 2002-2006.[8]

As mortality rates of first primary cancers continue to decrease, a greater number of cancer patients are expected to survive and become at risk for a second primary cancer that may prove fatal.[9] It is not clear whether the higher cancer mortality rate in Blacks would offset their higher cancer incidence rate, thereby resulting in a lower risk of second primary cancers compared with Whites. In other words, if Blacks have a higher incidence of first primary cancers than Whites, does it follow that they also have a higher rate of second primary cancers. Therefore, the proposed research project was undertaken to determine whether a first primary cancer in Blacks places them at a higher risk for developing a second primary cancer than a comparable first primary cancer in Whites.

Research Significance

Documenting the magnitude and temporal patterns of second primary cancers has implications for long-term surveillance and common etiologies between the first and second primary cancers. Comparing the incidence patterns of first and second primary cancers may point to explanations for the disparities between Blacks and Whites. Comparing clinical parameters of second primary cancers between Blacks and Whites may also reveal clues about the pathogenesis of cancer.

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Chapter 2: Background and Significance

Minimal data exists on second primary cancer incidence in Blacks and Whites as of April 2011. The SEER database now covers 26% of the US population (Table 1) and has grown to a size that renders the study of second primary cancer incidence in Blacks and Whites possible.

To qualify for analysis, a cancer site had to conform to the following criteria:

1) The first primary cancer had to be characterized by a relatively high overall 5-year survival rate ($\geq$ 60%).
2) The overall risk, specifically the Standardized Incidence Ratio (SIR) for the second primary cancer, defined as the ratio of observed cancer incidence among first primary cancer survivors over the expected occurrences in the general population, had to be significant ($\geq$ 1.1 and significant at the 95% level).
3) The power available for the competing risks survival analysis, which is the main analysis of this study, had to be sufficient to detect the minimal clinically significant risk ratio of 1.2 ($\geq$ 70%).
4) The chosen cancer site had to individually exhibit clinical and/or public health significance by afflicting a substantial proportion of the U.S. population and/or severely affecting the patient quality of life.

Based on the above-listed criteria, two common cancers, breast and colorectal cancer, were chosen as models for the study of second primary cancer incidence in Blacks and Whites.

Table 1 Number of Persons by Race, Gender, and Geographic Area for SEER Participants (2000 Census Data[1]), 1973-2007.

Total

	Total Population[2]	White[3]	Black[3]
Total US	282,194,308	230,556,812	36,726,368
SEER 09	26,793,306	20,573,478	3,262,044
SEER 13	38,965,674	29,591,385	4,404,889
SEER 17	73,836,260	57,933,821	8,427,181
SEER 9 % of US	9.5%	8.9%	8.9%
SEER 13 % of US	13.8%	12.8%	12.0%
SEER 17 % of US	26.2%	25.1%	22.9%

Females

	Total Population[2]	White[3]	Black[3]
Total US	136,099,410	116,848,094	19,251,316
SEER 09	12,075,290	10,367,488	1,707,802
SEER 13	17,166,715	14,855,756	2,310,959
SEER 17	33,560,498	29,173,665	4,386,833
SEER 9 % of US	4.3%	4.5%	4.7%
SEER 13% of US	6.1%	6.4%	6.3%
SEER 17 % of US	11.9%	12.7%	11.9%

Males

	Total Population[2]	White[3]	Black[3]
Total US	131,183,770	113,708,718	17,475,052
SEER 09	11,760,232	10,205,990	1,554,242
SEER 13	16,829,559	14,735,629	2,093,930
SEER 17	32,800,504	28,760,156	4,040,348
SEER 9 % of US	4.2%	4.4%	4.2%
SEER 13 % of US	6.0%	6.4%	5.7%
SEER 17 % of US	11.6%	12.5%	11.0%

[1]Source: U.S. Bureau of Census, Census 2000, Summary File 1, Table DP-1.

[2]Total Population equals the sum of the White, Black, American Indian/Alaska Native, Asian, Native Hawaiian/Pacific Islander, Other Race, and Two or More Races columns. Note that only the American Indian/Alaska Native populations are covered in the SEER areas of Arizona and Alaska.

[3]Since each person could report multiple races in the 2000 Census, race-specific counts and percentages in this table are based on persons self-reporting only one race.

Breast Cancer

Breast cancer remains the most commonly diagnosed malignant tumor among women. An estimated 261,100 new cases of breast cancer are expected among women in the US in 2010.[1] A large percentage of women diagnosed with breast cancer survive for an extended period of time. As of 2006, breast cancer has an overall 5-year survival rate of 89%.[2] However, breast cancer is associated with a significant excess risk of second primary cancers (Standardized Incidence Ratio (SIR): 1.25, 95% CI =1.24-1.26).[3,4] Breast cancer survivors suffer the highest burden of multiple primary cancers arising in the same site.[5] When considering prevalence of multiple primaries occurring in any site, female breast cancer ranks second to prostate cancer in men.[5] Higher risks of second primary breast, ovarian cancer, and uterine cancer have been reported after primary breast cancer (Table 2).[3,6-9]

Table 2 Second primary cancers following first primary female breast cancer.

Second Primary Cancer	**SIR**
Breast cancer	3.5* (95% CI = 3.2–3.8) [1]
Breast cancer, except contralateral breast cancer	1.25* (95% CI = 1.24-1.26)[2]
Endometrium	1.3 (0.9–1.8) [1] 1.52*,[2]
Ovaries	1.7*(95% CI = 1.2–2.3) [1] 1.48*,[2]

* Significant
[1] Soerjomataram et al., 2005
[2] Mellemkjaer et al., 2006

Furthermore, the burden of breast cancer is not spread equally among all groups (Table 3). In Black women, primary breast cancer occurring before age 45 is more common than in White women, and often is characterized by an earlier onset, more aggressive clinical presentation, and

less favorable survival.[10-13] After age 45, in contrast, the incidence of breast cancer decreases in Black women and is not as common as in White women.[12]

Table 3 Incidence, mortality, survival, and age at diagnosis patterns of first primary breast cancer.

	Whites	**Blacks**
Incidence (2003-2007) [1]	126.5	118.3
Mortality (2003-2007) [1]	23.4	32.4
Survival (1999-2006)	90.2	77.5
Age	61.0	57.0

[1] Incidence and death rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).
Source: http://seer.cancer.gov/csr/1975_2007

Despite the high prevalence of breast cancer and the increased risk of subsequent second primary cancers, only a limited number of studies have examined the pattern of second primary cancers among breast cancer survivors. In contrast with the Black-to-White incidence crossover among first primary breast cancers occurring around age 45, Black women were found to have a higher risk of subsequent breast cancers than white women.[12-14] Consistent with higher rates of first primary ovarian cancer among Whites than Blacks, second primary ovarian cancers have been found to be significantly more common among White than Black women.[14,15]

Colorectal Cancer

Colorectal cancer is the third most commonly diagnosed cancer in both men and women. An estimated 142,570 new cases of colorectal cancer are expected in 2010 (Table 4).[1] Colorectal cancer (CRC) survival at all stages has increased steadily over the past three decades among Black and White men and women in the U.S., most noticeably among White males (Table 5). [16-18] Incidence rates per 100,000 diagnoses of first primary CRC have also steadily decreased since the late 1990s but remain higher remain higher in men than women (Table 6).[18,19] While the risk of first primary CRC prior to 1985 was comparable in Blacks and Whites, the incidence rate of first primary CRC has been decreasing at a faster pace in Whites than in Blacks since the mid-1980s (Table 7).[18,20]

Table 4 Incidence, mortality, survival, and age at diagnosis patterns of first primary colorectal cancer.

	Whites	**Blacks**
Incidence (2003-2007) [1]	47.4	58.9
Mortality (2003-2007) [1]	17.1	24.7
Survival (1999-2006)	65.9	56.2
Age	71	65

[1] Incidence and death rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).
Source: http://seer.cancer.gov/csr/1975_2007

Table 5 CRC survival by year of diagnosis among Black and White, men and women.

		1975	2003	Absolute Difference	% Increase
White	**Male**	48.8	67.9	19.1	39.14
White	**Female**	49.4	65.7	16.3	32.99
Black	**Male**	40.4	53.8	13.4	33.17
Black	**Female**	44.5	59.3	14.8	33.26

Survival source: SEER 9 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).
Cancer sites include invasive cases only unless otherwise noted.

Table 6 CRC incidence by year of diagnosis and gender.

	2000	2008
Males	63.67	50.39
Females	46.73	39.22

Incidence source: SEER 13 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry and Rural Georgia).
Cancer sites include invasive cases only unless otherwise noted.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).

Table 7 CRC incidence by year of diagnosis in Blacks and Whites.

	1985	2007
Blacks	63.9	53.4
Whites	67.2	43.4

Incidence source: SEER 13 areas (San Francisco, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, Atlanta, San Jose-Monterey, Los Angeles, Alaska Native Registry and Rural Georgia).
Cancer sites include invasive cases only unless otherwise noted.
Rates are per 100,000 and are age-adjusted to the 2000 US Std Population (19 age groups - Census P25-1130).

The risk of second primary CRC, however, has been increasing since the early 1990s, in spite of a steady decline in the overall risk of first primary CRC since the late 1980s.[21] CRC survivors are at a 1.6 (95% CI=1.1–2.2) higher risk of a second primary CRC than the general population.[22]

Despite improved colorectal cancer survival and an increasing risk of second primary colorectal cancer since the early 1990s, second colorectal cancer incidence has not been studied in Black and White colorectal cancer female and male survivors. [16,17,21]

Study Hypothesis and Specific Aims

The proposed research was undertaken to determine whether a first primary breast or colorectal cancer in Blacks places them at a higher risk for developing of a second primary cancer than a comparable first primary cancer in Whites. The specific aims of this study were to:

i) Quantify the incidence rates of selected second primary cancers in Black and White breast and colorectal cancer survivors.

ii) Compare the demographic distributions and clinical characteristics of selected second primary cancers in the Black and White men and women.

iii) Infer putative risk factors for second primary cancers by comparing the patterns of first and second primary cancers in Blacks and Whites.

In the first manuscript, we reported the incidence of hormonally-related second primary cancers, specifically second primary breast, endometrial and ovarian cancers, following a first primary cancer of the breast in Black and White women. The second study compared the patho-epidemiological patterns of second primary contralateral breast cancers in Black and White women

to those of the first primary tumors. The third manuscript explored the incidence of second primary colorectal cancers in Black and White female and male survivors of a first primary colorectal cancer.

This research contributes to the scarce literature on second primary cancers following an initial primary breast and primary colorectal cancer. Documenting the magnitude and temporal patterns of second primary cancers has implications for long-term surveillance and common etiologies between first and second primary cancers. Comparing the incidence patterns of first and second primary cancers may point to explanations for the disparities between Blacks and Whites. Comparing clinical parameters of second primary cancers between Blacks and Whites may also offer clues about the pathogenesis of cancer.

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Chapter 3: Second Primary Breast, Endometrial, and Ovarian Cancers in Black and White Breast Cancer Survivors over a 35-year Time Span: Effect of Age

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ABSTRACT (Word Count= 236)

BACKGROUND: Breast cancer incidence increases with age and exhibits a Black-to-White crossover around age 45. Breast cancer survivors are at a significantly elevated risk of developing a second primary breast or gynecological cancer compared with the general population. The purpose of this study was to determine whether a similar crossover occurs in hormonally related second primary breast, endometrial, or ovarian cancers in Black and White women.

METHODS: The Surveillance, Epidemiology, and End Results' Registry 9 was used to follow 415,664 White and 39,887 Black female breast cancer survivors, diagnosed at age 19 or older, for a second primary breast, endometrial, or ovarian cancer between 1973 and 2007. Cumulative incidence curves were generated; Pepe and Mori's test was used to test for significance.

RESULTS: Second primary breast cancer followed the incidence pattern of the first primary breast cancer in Black and White women diagnosed before age 45. It was opposite of the pattern of first primary breast cancer in Black and White women diagnosed at age 45 or later. Second primary endometrial and ovarian cancers paralleled the incidence pattern of first primaries of the

same anatomic site among Black and White women, independent of the age at diagnosis of the first primary breast cancer.

CONCLUSION: Despite the Black-to-White crossover of first primary breast cancer around age 40, the incidence of hormonally related second primaries does not appear affected by the age at diagnosis of the first primary.

Keywords: Cumulative incidence • Breast cancer • Second primary cancer • Age • Race

INTRODUCTION

Complex relationships seem to prevail among carcinomas of the breast, endometrium, and ovary. Breast and endometrial cancer have both been associated with hyper-estrogenic activity.[1] Tamoxifen, an antagonist of the estrogen receptor in breast tissue, has been effective in preventing and treating some cases of post-menopausal breast cancer, yet it may stimulate endometrial tissue, leading to carcinoma.[2-5] Not only does ovariectomy reduce the probability of developing breast cancer, the procedure has also been used for its therapeutic effect on breast cancer.[6-8] Although we believe these relationships depend on hormonal activity, other factors may also be at play. For example, breast cancer has a higher incidence and is more aggressive in young Black women less than 45 years of age than in White women, but has a lower incidence in Black than in White women after 45 years of age.[9-11] Inflammatory breast cancer and medullary carcinoma are more common in Black women before age 45 than in White women.[12-14] Although Black women have a lower incidence of breast cancer compared with White women after age 45, they have lower survival rates and usually a later stage at presentation.[14,15] Black women also have a significantly lower incidence of ovarian cancer at all ages than White women, and ovarian tumors of low malignant potential seem to carry a lower risk of subsequent breast cancer compared to the general population.[16,17] Further, Black women similarly have a significantly lower incidence of endometrial cancer at all ages than White women, and hysterectomy appears to decrease the risk of subsequent ovarian but not breast cancer.[6,18,19] As a means to explore the complex interrelationships between breast, endometrial and ovarian cancers, this study was undertaken to determine whether these hormonally related second primary cancers exhibit a similar Black-to-White crossover as the first

primary breast cancer. The findings of this study have implications for the screening of second cancers in breast cancer survivors and may offer clues about their etiology.

SUBJECTS AND METHODS

Study Population

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Registry 9 database was used to follow a total of 455,551 women, 415,664 (91.2%) White and 39,887 (8.8%) Black female breast cancer survivors, diagnosed at age 19 or older, for the occurrence of a second primary cancer between 1973 and 2007. SEER's registry 9 covers 8.8% and 9.0% respectively of the Black and White populations. Chosen for their epidemiologically significant population subgroups, SEER regions are reasonably representative of the racial diversity of the US.[20] Racial identity was determined using a combination of medical records, physician and nursing notes, photographs, and any other available sources. According to SEER, a second primary cancer was defined as one that arises independently in a new anatomic site or tissue at least two months subsequent to the diagnosis of the first primary cancer, or arises in the same primary anatomic site but has a histopathology different from the first primary cancer.[21] In situ carcinomas and all histological types were included.

Statistical Methods

Data were compiled using SEER*Stat's Multiple Primary -- Standardized Incidence Ratios (MP-SIR) session and imported into SAS. They were stratified into two age groups (<45 years and >= 45 years) to approximate the White-to-Black incidence crossover.[9] Cumulative Incidence Function (CIF) curves, which account for competing events, were generated to describe among first primary

breast cancer survivors, the probability of developing a second primary cancer overall, and of developing a second primary cancer of the breast, endometrium, or ovaries following first primary breast cancer.[22,23] Pepe and Mori's test, which is a two-sample test of the equality of two CIFS, was used to test for significant differences in cumulative incidence of second primary cancers by race.[24] Subjects were censored at the date last known to be alive (12,864; 2.8%), or SEER follow-up cutoff date of 2007 (218,748; 48.0%), whichever came first. Death (169,232; 37.1%) and the occurrence of specific second primary cancers (54,707; 12.0%) depending on the analysis were treated as competing events. Second breast cancers which arise within 2 years of the diagnosis of the first breast cancer are thought to represent recurrences of the disease more often than independent primaries arising in the same organ.[25] To decrease the potential for breast cancer recurrences, a sensitivity analysis was conducted excluding second primary breast cancers which arose within 2 years following the first primary breast cancer. There has been an increasing trend of breast cancer incidence that started in the early 1980s when mammography was introduced.[26] To investigate its effect on second primary breast cancers, incidence rates across our study period (1973-2007) were compared to those restricted to the later decades when mammography was introduced (1980-2007); this was evaluated in each of the four age-race specific subgroups (Blacks diagnosed <45, Blacks diagnosed ≥45, Whites diagnosed <45, Whites diagnosed ≥45). SEER*Stat 6.2.2 and SAS 9.2 were used for all analyses.

RESULTS

All Anatomic Sites

A total of 54,707 second primary cancers in all anatomic sites were observed among 450,936 women who had survived 2 months or more after an in situ or invasive breast cancer diagnosed

during 1973-2007. The majority of first primary breast cancers (390,888; 85.8%) occurred in women 45 years of age or older. The majority of second primary cancers, 48,244 (88.2%) cases, also occurred in women diagnosed with a first primary cancer at age 45 or older. Among first primary breast cancer survivors, 10.9% (4,360) of Blacks and 12.1% (5,034) of Whites developed a second primary cancer. Among all second primary cancers, 40.7% (22,290) occurred in the breast, 6.99% (3,827) in the endometrium, and 3.4% (1,867) in the ovaries. The remaining second primary cancers occurred in the lung (10.8%) and other anatomic sites (38.0%). The median interval in years between the first primary breast cancer and any second primary cancer was shorter in Blacks than Whites (Table 1).

A number of patients with primary breast cancer may die from a competing risk of death prior to developing a second cancer. Therefore, to account for the competing risk, the cumulative incidence of developing a second cancer was estimated. The cumulative incidence of second cancers of all anatomic sites was significantly higher in Blacks than Whites among women diagnosed with a first primary cancer before age 45 (p=0.00087). However, there was no significant difference in the cumulative incidence between Whites and Blacks among women diagnosed with a first primary cancer at age 45 or older (Figure 1). Cumulative incidence estimates of second primary cancers in all anatomic sites 25 years following the diagnosis of the first primary breast cancer are presented in Table 2.

Breast

Second primaries following a first in situ or invasive primary breast cancer occurred most frequently in the breast (22,290; 40.7%). Of those, 90.8% (20,231) were diagnosed among Whites and 9.2% (2,059) in Blacks. The majority of second primary breast cancers, 18,227 (81.7%) cases,

occurred in women diagnosed with a first primary breast cancer at age 45 or older. They included ipsilateral and contralateral second primary breast cancers. Blacks had a shorter median interval in years between the first and a second primary breast cancer (Table 1).

Second primary breast cancer incidence rates across the study period did not differ from those restricted to the later decades when mammography became available for any of the four age and race subgroups. Therefore, second primary breast cancer incidence rates were considered between 1973 and 2007. The cumulative incidence of developing a second primary breast cancer was significantly higher among Blacks than Whites for women diagnosed with an initial primary breast cancer before age 45 ($p<0.000001$), or at age 45 and older ($p= 0.00003$) (Figure 2). The difference between the Black and White CIFs was greater in women diagnosed before age 45 than among women diagnosed at age 45 or later. Even after eliminating the possibility of recurrences by excluding second primary breast cancers arising within 2 years following the first primary breast cancer, our results remained unchanged.[25] Cumulative incidence estimates of second primary breast cancer 25 years following the diagnosis of the first primary breast cancer are presented in Table 2.

Endometrium

A total of 3,827 second corpus uterine cancers were diagnosed among first primary Breast cancer survivors, representing 6.99% of all second primary cancers. Of those, 94.4% (3,612 cases) were among Whites and 5.6% (215) were among Blacks. The majority of second primary endometrial cancers, 3,552 (92.8%) cases, occurred in women diagnosed with the first primary breast cancer at

age 45 or later. The median interval in years between the first primary breast cancer and a second primary endometrial cancer was shorter in Whites than in Blacks (Table 1).

The cumulative incidence of developing second endometrial cancer following a first primary breast cancer diagnosis was significantly higher for Whites than Blacks in women diagnosed before age 45 ($p=0.00004$), and at age 45 or later ($p< 0.05$) (Figure 3). Cumulative incidence estimates of second primary endometrial cancer 25 years following the diagnosis of the first primary breast cancer are presented in Table 2.

Ovary

Among second primary cancers diagnosed in first primary Breast cancer survivors, 3.41% (1,867) occurred in the ovaries. Of those, 95.2% (1,778) were diagnosed among Whites and 4.8% (89) among Blacks. The majority of second primary ovarian cancers, 1,569 (84.0%) cases, occurred in women diagnosed with the first primary breast cancer at age 45 or later. Blacks had a shorter median interval in years than Whites between the first primary breast cancer and second primary ovarian cancer (Table 1).

The cumulative incidence of a second primary ovarian cancer was significantly higher in Whites than in Blacks, among women diagnosed before age 45 ($p=0.00074$), and at age 45 or later ($p=0.00008$) (Figure 4). Cumulative incidence estimates of second primary endometrial cancer 25 years following the diagnosis of the first primary breast cancer are presented in Table 2.

DISCUSSION

This study has compared the cumulative incidence and timing of second primary cancers arising in the breast, endometrium, or ovary in Black and White women over 35 years following an initial first primary cancer of the breast. Specifically, its purpose was to determine whether these hormonally related second primary cancers exhibit a crossover similar to that observed in first primary breast cancer among Blacks and Whites.

In contrast with the Black-to-White incidence crossover among first primary breast cancers, the incidence of second primary ipsilateral or contralateral breast cancers was significantly higher among Black than White breast cancer survivors, independent of the age at diagnosis of the initial primary breast cancer. Results remained unchanged even when the possibility of recurrences was reduced. This observation seems to reflect a number of possibilities which in general are difficult to resolve. It is possible that Blacks have higher rates of second primary cancers than Whites in the ipsilateral breast, although some of these cancers may be recurrences. It may be that Blacks are truly more prone to second primary cancers in the ipsilateral and contralateral breasts. It is also possible that Blacks may be more prone to bilateral breast cancer with the contralateral cancer presenting later that the first cancer. Nonetheless, it seems unusual that Blacks who have a lower incidence of post menopausal breast cancer than Whites have a higher rate of second primary breast cancers than Whites in the post menopausal period.

The incidence of endometrial second primary cancers was significantly higher among White than Black women, regardless of age at diagnosis of the first breast cancer. This is opposite of the pattern seen for first and second primary breast cancer but is consistent with the reported lower incidence of first primary gynecologic cancers among Blacks compared with Whites.[18] Black

women are known to have higher rates of hysterectomies for benign conditions compared with White women, which precludes the development of a second primary corpus uterine cancer.[27-29] It is possible that the higher hysterectomy rates in Blacks artifactually contribute to their lower second primary endometrial cumulative incidence rates in comparison to Whites. In addition, Tamoxifen (Nolvadex®) has been implicated in the development of second primary endometrial cancers in breast cancer survivors.[4,5] It is also more commonly used for the treatment of regional-stage disease in Whites than Blacks.[30] It is possible that the difference in Tamoxifen treatment between the two groups, likely resulting from the higher prevalence of ER+ breast cancers among Whites than in Blacks, contributes to the higher cumulative incidence of second endometrial primaries among White compared with Black women. The extent of this contribution is however expected to be limited because of the low absolute risk of Tamoxifen-related second primary corpus uterine cancer.

Second primary ovarian cancers were significantly more common among White than Black women, regardless of the age at diagnosis of the first primary breast cancer. This is consistent with previous reports of a higher incidence of second ovarian cancers among White compared with Black breast cancer survivors.[31] It also parallels the reported lower incidence of first primary gynecologic cancers among Blacks compared with Whites.[18] The prevalence of BRCA1, which is associated with an increased risk of breast and ovarian cancers, is higher in White than in Black women. It is possible that the increased incidence of ovarian cancer could be in part a reflection of the higher prevalence of BRCA1.[32]

This study has limitations typical of a descriptive epidemiologic study using the SEER database. The accuracy of the second cancer incidence rates is dependent on SEER's coding rules for multiple primaries. Other organizations such as the International Association for Cancer Registries (IACR) have different definitions which may not be congruent with SEER's definition. Consequently, analyses using different definitions may yield dissimilar results. The interpretation of the incidence estimates may be affected by the limited treatment information available in SEER which affects survival and consequently the incidence of seconds. They could also be underestimated as a result of SEER population mobility. While our results were stratified by age, we did not test for an age by race interaction due to the size of the SEER dataset and limitations in computing resources. As the only national cancer registry in the US, SEER incidence rates have not been validated for representativeness of Blacks and Whites, however they are commonly used to estimate national estimates of cancer incidence among subgroups in the US.[33,34] Nevertheless, SEER is a large population based cancer registry with over 35 years of follow-up. It uses a combination of active and passive follow-up to ascertain cancer incidence. Combined with its relatively low rate of race status misclassification in comparison with other cancer registries, SEER is especially appropriate for the study of second cancer incidence rates by race.[35,36]

In summary, this study describes the cumulative incidence and timing of second primary cancers of the breast, endometrium, and ovaries following a first primary breast cancer in Black and White women across 35 years. Despite the Black-to-White crossover exhibited by first primary breast cancer at age 40, hormonally related second primaries did not appear affected by the age at diagnosis of the first primary. The cumulative incidence of second primary breast cancer was significantly higher in Blacks than White, whereas the cumulative incidence of second primary

endometrial and of second primary ovarian cancer was significantly higher among Whites than Blacks.

As breast cancer patients survive longer, higher vigilance by clinicians in screening cancer survivors for second cancers is warranted.

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Table 1 Median number of years between the diagnosis of the first primary breast cancer and the second primary cancer, by cancer site and age at diagnosis of the first primary breast cancer in Black and White women.

	<45		≥45	
Site of second primary cancer	**Black**	**White**	**Black**	**White**
All sites	6.57	8.24	5.16	5.83
Breast cancer	5.91	6.99	4.66	5.75
Endometrial cancer	11.19	8.82	6.08	5.41
Ovarian cancer	4.07	8.83	3.33	5.49

[1] A test of statistical significance is not provided because it does not account for the competing risk of mortality.

Table 2 Cumulative incidence estimates of second primaries by cancer site 25 years following the diagnosis of the first primary breast cancer in Black and White women.

	All Ages		**1st Primary Breast Cancer < 45**		**1st Primary Breast Cancer ≥ 45**	
	Blacks	**Whites**	**Blacks**	**Whites**	**Blacks**	**Whites**
2nd Primary Cancer (95% CI)	19.2% (18.6 –19.8)	19.6% (19.4-9.7)	18.1% (16.7-19.5)	17.4% (16.9-17.9)	19.5% (18.8-20.3)	19.9% (19.7-20.1)
2nd Primary Breast Cancer (95% CI)	8.7% (8.3 – 9.1)	7.7% (7.6-7.8)	11.8% (10.8-12.9)	9.9% (9.5-10.3)	7.7% (7.3-8.2)	7.3% (7.2-7.5)
2nd Primary Endometrial Cancer (95% CI)	1.0% (0.9 – 1.2)	1.35% (1.3-1.4)	0.7% (0.4-1.2)	0.9% (0.8-1.0)	1.1% (0.9-1.3)	1.4% (1.4-1.5)
2nd Primary Ovarian Cancer (95% CI)	0.4% (0.3-0.5)	0.68% (0.6-0.7)	0.003 (NA)	0.9% (0.8-1.0)	0.3% (0.3-0.5)	0.65% (0.6-0.7)

Figure 1 Cumulative incidence of any second primary cancer among Black and White women diagnosed with a first primary breast cancer before age 45, or at age 45 or older, 1973-2007.

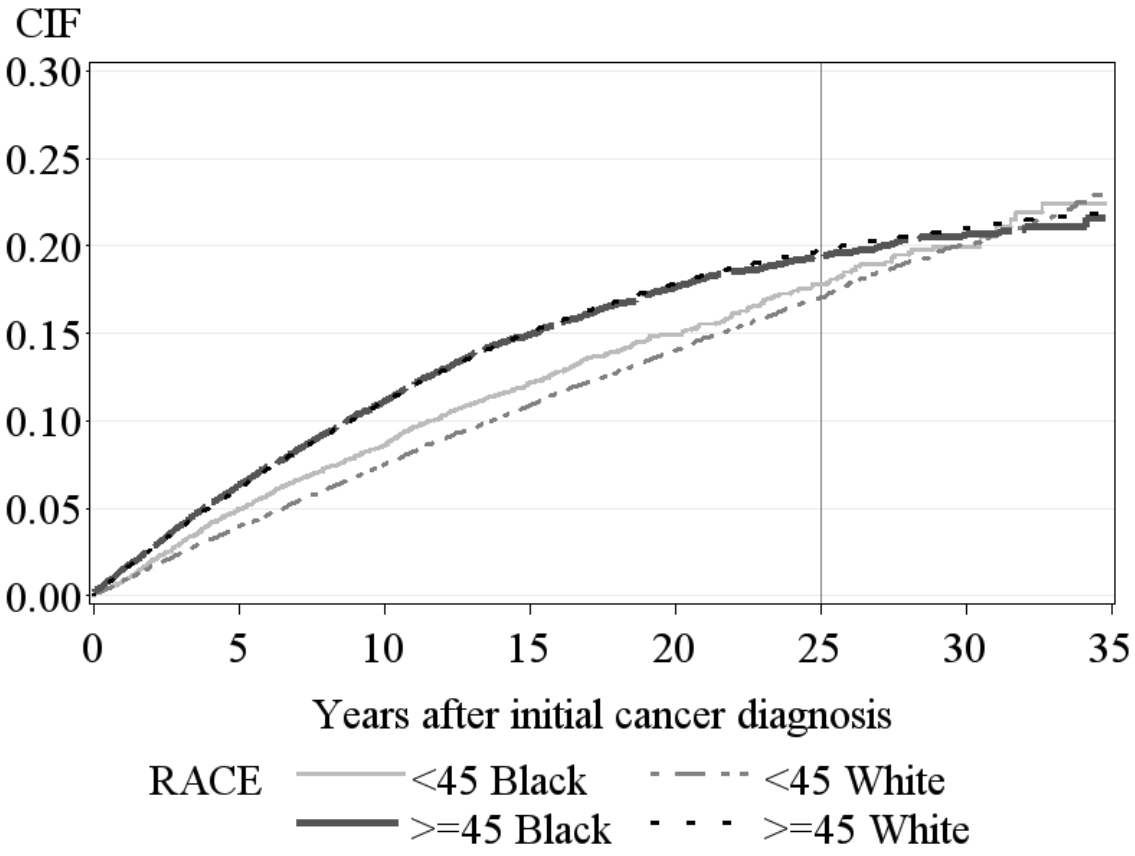


Figure 2 Cumulative incidence of second primary breast cancer among Black and White women diagnosed with a first primary breast cancer before age 45, or at age 45 or older, 1973-2007.

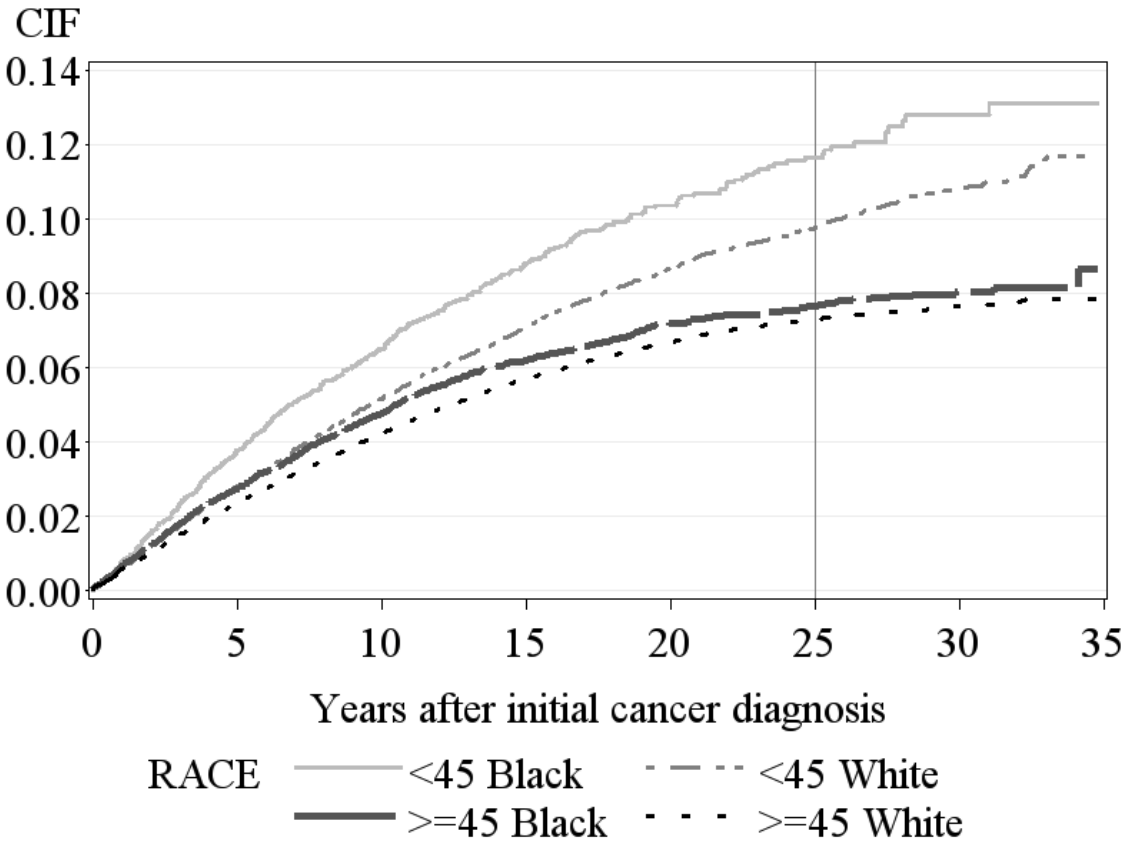


Figure 3 Cumulative incidence of second primary endometrial cancer among Black and White women diagnosed with a first primary breast cancer before age 45, or at age 45 or older, 1973-2007.

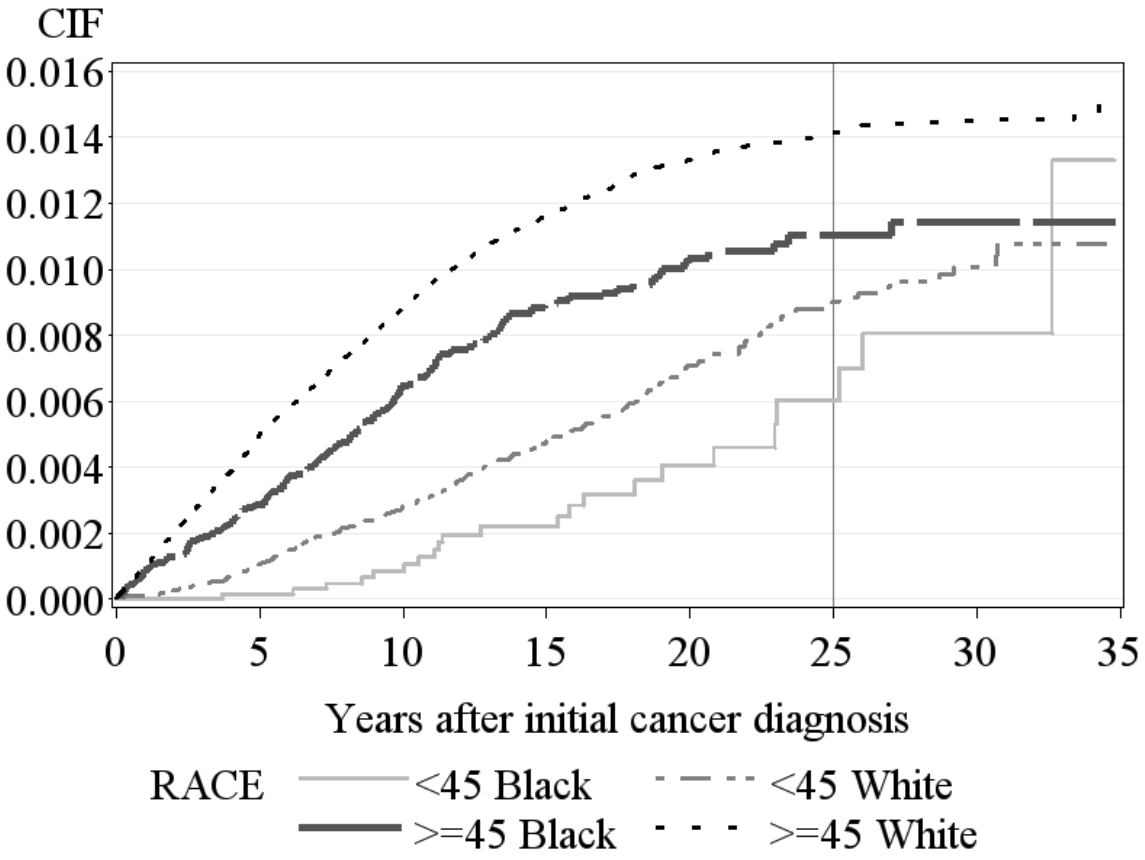
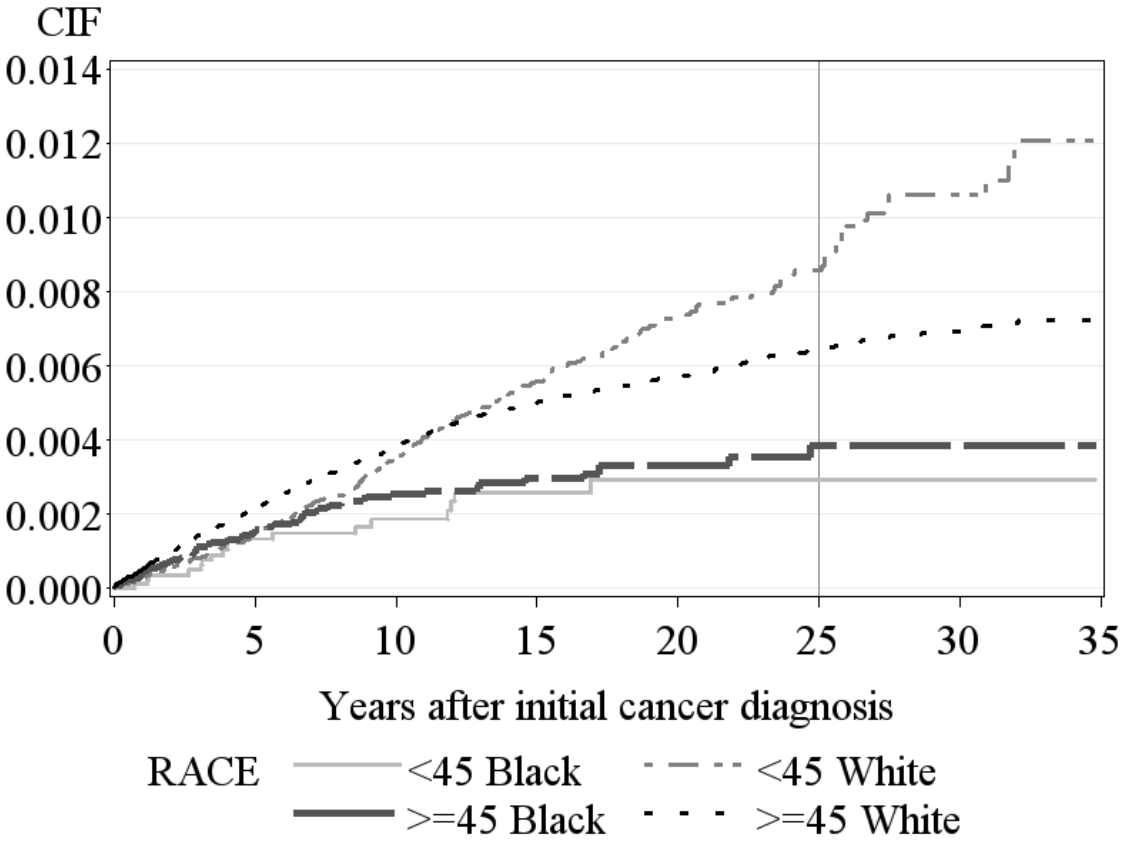


Figure 4 Cumulative incidence of second primary ovarian cancer among Black and White women diagnosed with a first primary breast cancer before age 45, or at age 45 or older, 1973-2007.



Chapter 4: Patho-Epidemiological Patterns of Contralateral Breast Cancers in Black and White Women

ABSTRACT (Word Count= 274)

BACKGROUND: Women with one primary breast cancer are at greater risk for developing a second cancer in the contralateral breast, despite the protective effect of Tamoxifen treatment. Breast cancer exhibits a Black-to-White incidence crossover at age 40. The purpose of this study was to investigate whether the patho-epidemiological patterns of second primary contralateral breast cancers in Black and White women are similar to those of the first primary tumors according to age at diagnosis of the first primary breast cancer.

METHODS: The Surveillance, Epidemiology, and End Results' (SEER) Registry 9 database was used to follow a total of 455,551 women, 415,664 White (91.24%) and 39,887 Black (8.76%) female breast cancer survivors, diagnosed at age 19 or older, for the occurrence of a second primary contralateral breast cancer between 1973 and 2007. Black and White women with a first primary in-situ or invasive breast cancer and a second primary contralateral breast cancer (n= 18,142) were analyzed by age at diagnosis, histologic tumor type, histological grade, tumor size, tumor markers, and number of positive lymph nodes. The cumulative incidence of a second contralateral breast cancer, which accounts for the competing risks of death and second non-breast cancers, was also explored among Black and White breast cancer survivors.

RESULTS: Second contralateral breast cancers in Black women were characterized by an earlier onset, higher incidence, and more aggressive clinical presentation than in Whites. In contrast to first primary breast cancers, second primary breast cancers are more common in Black than in White women of all ages.

CONCLUSION: Our results point to the possible bilaterality of many cases of breast cancer, and to a possible shared etiology between cancers in the two contralateral breasts.

Keywords: Contralateral Breast cancer • Age • Race

BACKGROUND

Breast cancer remains the most commonly diagnosed cancer among females. An estimated 261,100 new cases of breast cancer are expected among women in the US in 2010.[1] A large percentage of women diagnosed with breast cancer survive for an extended period of time. For example, as of 2006, breast cancer has an overall 5-year survival rate of 89%.[2] Breast cancer survivors however, suffer the highest burden of multiple primary cancers arising in the same site.[3] Women with one primary breast cancer are at an increased risk for developing a second primary cancer in the contralateral breast, despite the protective effect of Tamoxifen treatment which is known to reduce the occurrence of contralateral breast cancer.[4-7] According to the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute (SEER), at least 4.0% of women with a primary breast cancer develop a second primary cancer in the contralateral breast.

The burden of breast cancer, however, is not spread equally among all groups. In Black women, primary breast cancer occurring before age 45 is more common than in White women. After age 45, in contrast, the incidence of breast cancer in Black women is not as common as in White women.[8] Compared to White women, Black women are more likely to be diagnosed at an earlier age with breast tumors that are less differentiated, hormone receptor negative, large, metastatic, and lymph node-positive.[8-12]

The purpose of this study was to investigate whether the patho-epidemiological patterns of second primary contralateral breast cancers in Black and White women are similar to those of the first primary tumors, and whether the patho-epidemiological patterns of the first and second contralateral primary breast cancer differ between Blacks and Whites. By comparing the patterns

between the clinical parameters of the two contralateral cancers in Black and White women, the findings of this study may offer clues about the pathogenesis of bilateral breast cancer.

SUBJECTS AND METHODS

Study Population

The National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) Registry 9 database was used to follow a total of 455,551 women, 415,664 (91.2%) White and 39,887 (8.8%) Black female breast cancer patients, diagnosed at age 19 or older, for the occurrence of a second primary cancer between 1973 and 2007. SEER's registry 9 covers 8.8% and 9.0% respectively of the Black and White populations. Chosen for their epidemiologically significant population subgroups, SEER regions are reasonably representative of the racial diversity of the US.[13] SEER determines racial identity using a combination of medical records, physician and nursing notes, photographs, and any other available sources. According to SEER, a second primary cancer was defined as one that arises independently in a new anatomic site or tissue at least two months subsequent to the diagnosis of the first primary cancer, or arises in the same primary anatomic site but has a histopathology different from the first primary cancer. Ipsilateral second primaries, 4,042 cases, were excluded to eliminate the possibility of recurrences. Both in situ and invasive carcinomas were included.

Statistical Methods

Data were compiled using SEER*Stat's Multiple Primary -- Standardized Incidence Ratios (MP-SIR) session and imported into SAS. Data were stratified into two age groups (<45 years and >=

45 years) to approximate the White-to-Black incidence crossover.[8] Black and White women with a first primary in-situ or invasive breast cancer and a second primary contralateral breast cancer were analyzed by age at diagnosis, histologic tumor type, histologic grade, tumor size, tumor markers, and number of positive lymph nodes. The Van Der Waerden test was used to compare the distributions of continuous clinical characteristics of the first primary breast cancer and of the second primary contralateral breast cancer, between Black and White women. The paired T-test or its non-parametric equivalent, the Wilcoxon signed-rank test, was used to compare the distributions of paired continuous variables between the first primary and the second primary contralateral breast cancers, within White and within Black women separately. McNemar's test was used to examine the association of the first primary and second primary contralateral breast cancers with respect to a paired categorical variable with two levels, within White and within Black women separately; Bhapkar's test was used instead when the variable had more than two level.[14] The standardized incidence Ratio (SIR) was used to quantify the risk of specific histologic types in comparison to the US general population.[15] Cumulative Incidence (CI) curves, which account for competing events, were generated to describe, among first primary cancer breast cancer survivors, the probability of developing a second primary breast cancer. [16] Pepe and Mori's test, which is a two-sample test of the equality of two cumulative incidence functions, was used to test for significant differences in cumulative incidence of second contralateral breast cancers by race. [17]

There has been an increasing trend of breast cancer incidence that started in the early 1980s when mammography was introduced. [18] To investigate its effect on second primary breast cancers, incidence rates across our study period (1973-2007) were compared to those restricted to the later decades when mammography was introduced (1980-2007); this was evaluated in each of the four age-race specific subgroups (Blacks diagnosed <45, Blacks diagnosed ≥45, Whites diagnosed <45,

Whites diagnosed ≥45). Subjects were censored at the date last known to be alive (12,864; 2.8%), or SEER follow-up cutoff date of 2007 (218,748; 48.0%), whichever came first. Death (169,232; 37.1%) and the occurrence of non-breast second primary cancers (32,417; 7.1%) were treated as competing events. Laterality, which refers to the side of the breast in which the symptoms of the cancer are manifested, was not reported for 106 (0.02%) women. Breast cancer survivors who were diagnosed with a second primary ipsilateral cancer were excluded (n=4,042). Based on their availability, completeness, and ease of consolidation across time, tumor makers and grade were used starting 1990, number of lymph nodes starting 1988, and tumor size starting 1983; all other parameters were used starting 1973. SEER*Stat 6.2.2 and SAS 9.2 were used for all analyses.

RESULTS

A total of 18,142 second primary contralateral breast cancers, all of which were invasive, were observed among 450,936 women who had survived 2 months or more after an insitu (59,580; 13.1%) or invasive (39,5971; 86.9%) breast cancer diagnosed during 1973-2007. Of those, 3.9% (1,578) of Black and 4.0% (16,564) of White women developed a second contralateral breast cancer. Second primary contralateral breast cancers were more common among women diagnosed with a first primary breast cancer after age 45 (15,101; 83.2%) than at or before age 45.

Cumulative Incidence

A number of patients with primary breast cancer may die or develop a second primary cancer prior to developing a second primary contralateral cancer. Therefore, to account for the competing risk, the cumulative incidence of developing a second primary contralateral cancer was estimated. Since second primary breast cancer incidence rates across the study period did not differ from those

restricted to the later decades when mammography became available for any of the four age and race subgroups, they were considered between 1973 and 2007. The cumulative incidence of developing a second primary contralateral breast cancer was significantly higher among Blacks than Whites for women diagnosed with an initial primary breast cancer before age 45 ($p < 0.00001$), or at age 45 and older ($p = 0.00003$) (Figure 1). The difference between the Black and White cumulative incidence curves was greater in women diagnosed before age 45 than among women diagnosed at age 45 or later. Cumulative incidence estimates of second primary contralateral breast cancer 25 years following the diagnosis of the first primary breast cancer are presented in Table 1.

Time Elapsed

The median interval between the first primary and second contralateral breast cancer was shorter in Blacks than in Whites, regardless of age at diagnosis of the first primary cancer (Table 1). Among Whites and Blacks, 25.0% and 29.8% respectively had a second primary contralateral tumor arise within two years of diagnosis of the first primary breast cancer. The number of diagnosed second contralateral cancers was highest at one year for both Whites 11.2% (1,858) and Blacks 13.2% (208) (Figure 2).

Age at Diagnosis

The median age at diagnosis of the second primary contralateral breast cancer was significantly lower in Blacks (59) than Whites (67) ($p < 0.0001$) (Figure 3). It was similarly lower in Blacks (52) than Whites (59) for the first primary breast cancer.

Histologic Tumor Type

Ductal carcinoma was the most common histologic type of first primary (12,856; 70.9%) as well as second primary contralateral (13,362; 73.6%) breast cancers, independent of age at diagnosis of the first primary cancer in both Black and White women.

Among women diagnosed with a first primary lobular breast cancer at age 45 or later, the risk of a lobular contralateral breast cancer was significantly elevated compared to the general population (Table 2). It was higher than the corresponding risk of a second ductal following a first primary lobular cancer in comparison to the general population (Table 2), despite the decreasing rate of lobular breast cancer in women ages 45 and older (Milanese et al., 2006). This was consistent among women diagnosed with a first primary cancer before age 45 (Table 2).

Among women diagnosed with a ductal first primary breast cancer at age 45 or later, the risk of a ductal contralateral breast cancer was significantly elevated compared to the general population (Table 2). The overall SIR, representing Blacks and Whites combined, was also higher than the corresponding risk of a second lobular following a first primary ductal breast cancer (Table 2). This was consistent among women diagnosed with a first primary cancer before age 45 (Table 2).

Our findings therefore show that the likelihood of concordant histology in ductal or lobular breast cancer is higher than discordant occurrence.

Histologic Grade

Only 38.8% (2,299) of second primary contralateral breast cancers had the same grade as the first primary breast cancer. Second primary contralateral breast cancers presented at a higher grade compared with the first primary breast cancer among Black and White women diagnosed before age 45 ($p_{Black} < 0.0001$, $p_{White} < 0.0001$) and at age 45 or later ($p_{Black} < 0.0001$, $p_{White} < 0.0001$).

Furthermore, among women diagnosed before age 45 ($p < 0.0001$) and at age 45 or later ($p < 0.0001$), Black women presented with higher grade second contralateral cancer compared with White women (Table 1). Our results therefore show that second primary contralateral cancers are more likely to be aggressive than the first primary cancer, and among Blacks than in Whites.

Tumor Size

Within Blacks ($p<.0001$) and in Whites ($p <.0001$), the median tumor size of the contralateral breast cancer measured significantly less than that of the first primary breast cancer (Table 1). This pattern was consistent independent of the time elapsed between the first primary and second contralateral breast cancers. The median diameter of the second contralateral breast cancer was significantly higher in Black than in White women ($p <.0001$). Second contralaterals in Blacks and Whites diagnosed with a first primary breast cancer before age 45 were significantly larger than those diagnosed in Blacks and Whites diagnosed at age 45 or later respectively ($p_{Blacks}<0.0001$; $p_{Whites}<0.0001$). Our findings may suggest that second primary contralateral cancers were diagnosed at a later time than could have been detected in the presence vigilant medical surveillance. They may also reflect an aggressive second primary contralateral tumor with a high growth rate.

Tumor Markers

Estrogen Receptor

The majority of second primary contralateral breast cancers (3,376; 73.9%) had the same estrogen receptor status as the first primary breast cancer ($p=0.15$). Among women diagnosed with a first primary breast cancer before age 45, the majority of first primary and of second contralateral breast

cancers were ER+ in Whites and ER- in Blacks. Among Black and in White women diagnosed with a first primary breast cancer at age 45 or later, the majority of first primary and of second contralateral breast cancers were ER+ (Table 1).

Progesterone Receptor

The majority of second primary contralateral breast cancers (2,701; 61.7%) had a different progesterone receptor status than the first primary breast cancer ($p<.0001$). Among women diagnosed with a first primary breast cancer before age 45, the majority of first primary and of second contralateral breast cancers were PR- in Blacks. First primary and second contralateral breast cancers in White women diagnosed with a first primary breast cancer before age 45 were evenly distributed between PR-positive and PR-negative statuses. The majority of first primary and second contralateral breast cancers in Whites as well as first primary breast cancers in Blacks among women diagnosed with a first primary breast cancer at age 45 or later were PR-positive. However, second contralateral breast cancers among Black women diagnosed at age 45 or later were evenly divided distributed PR-positive and PR-negative status (Table 1).

Lymph Nodes

The majority of examined first primary (4,935;70%) and of second contralateral breast cancer lymph nodes (8,184;72.29%), were negative. Second contralateral breast cancers in women diagnosed with a first primary breast cancer before age 45 were characterized by a significantly higher number of positive lymph nodes than women diagnosed at age 45 or later ($p=0.03$). The number of positive nodes did not significantly differ between Black and White women. There also was no significant difference in the number of positive lymph nodes between the second

contralateral breast cancer and the first primary breast cancer within Blacks and within Whites (Table 1).

Exponential Tumor Growth

To estimate whether the contralateral breast cancer already existed at the time the first cancer was diagnosed, we used the exponential model of tumor growth. The mean tumor diameter in centimeters at diagnosis of a second primary averaged 2.6 ± 1.79 in Blacks and 2.07 ± 1.51 in Whites. About half of all second contralateral breast cancers in SEER were diagnosed within 6 years of the first primary breast cancer. The time it takes a breast cancer to double varies; however, it is estimated to be 84 days for BRCA1/2 mutation carriers.[19] Further, it is estimated that it takes 30 cell doublings for a 1 centimeter (cm) tumor to form. [20] Using the above assumptions, we found that it would take a 2 cm tumor an excess of 10 years to grow. Since the accuracy of mammography in detecting tumors < 2 cm in size drops considerably, our findings suggest that second contralateral cancer may have been initially present around the time of diagnosis of the first primary breast cancer but too small for detection.

DISCUSSION

The patho-epidemiology pattern of breast cancer in Black and White women is based on the analysis of primary breast cancer in both groups.[8] Black women have a higher risk of breast cancer before age 45, present with more aggressive tumors, and have less favorable survival rates.[8,10-12,22,23] After age 45, Black women have a lower risk of breast cancer than Whites.[8] However, as we have shown, this relationship does not hold for second primary cancers occurring in the contralateral breast.

The higher rate of a second contralateral cancer in Black women after age 45 does not follow the epidemiologic data that shows a lower rate of breast cancer in Black women compared to white women after this age. This may indicate a higher susceptibility to breast cancer in some Black women. However, tumor growth calculations based on the exponential model showed that these cancers were most likely in existence when the first cancer presented. Since breast cancers are more common in Black women before age 45, this higher rate of contralateral cancers most likely reflects the higher rate in Black women of the first cancer before age 45.[8] All of the second contralateral breast cancers exhibited invasive behavior, despite a small proportion (16.8%) of in situ first primary breast cancers in our study. This observation further suggests that second contralateral cancers may have been initially too small for detection and later diagnosed at a more advanced stage. We should also mention that Black women have a higher rate of ER- breast cancers in the primary and in the contralateral breasts compared to White women before age 45. [21,24] The congruence in ER status suggests that a high proportion of these contralateral cancers were initiated about the same time as the first cancer before age 45, but presented later.

The likelihood of concordant second contralateral breast cancer histology was higher than that of a discordant occurrence. This observation has been corroborated in earlier studies. [25] This was true for ductal histology, and also for lobular histology, despite lobular involution in older women. Our finding suggests shared etiology between the cancers of this paired organ. Thus, we speculate that the histopathology of the second tumor is not a random event, but related to the first.

Consistent with the higher incidence of second primary breast cancers among Blacks compared to Whites, women of African descent (15.6%) have a significantly higher prevalence of deleterious BRCA1 and BRCA2 mutations compared with women of Western European ancestry (12.1%). This is thought to be primarily because of an increased prevalence of BRCA1 mutations. [26] In

conformity with the higher incidence of second primary breast cancers among Blacks compared to Whites especially among women with a first primary breast cancer diagnosed before age 45, BRCA1 mutations are particularly high among young (<35 years) African American patients 16.7%.[27] We suspect that BRCA1/2 mutations, among other environmental factors, represent a significant aspect of the common etiology between cancers of the two breasts.

This study has limitations typical of a descriptive epidemiologic study using the SEER database. The accuracy of our second cancer incidence rates is dependent on SEER's coding rules for multiple primaries. Other organizations such as the International Association for Cancer Registries (IACR) have different definitions which are not congruent with SEER's definition. [28] Consequently, analyses using different definitions may yield dissimilar results. The incidence estimates are potentially impacted by the limited treatment information available in SEER which affects survival and consequently the incidence of seconds. They could also be underestimated as a result of SEER population mobility. The classification systems of the breast cancer clinicopathological characteristics such as stage, tumor markers, lymph nodes, and tumor size have changed across our study period. As a result, we used broader categories to consolidate the variables across time, the effect of which is not known, but expected to be minimal. Owing to the missing values in some clinical parameters, our conclusions assume the unknown values followed a similar distribution as the known values. While our results were stratified by age, we did not test for an age by race interaction due to the size of the SEER dataset and limitations in computing resources. As the only national cancer registry in the US, SEER incidence rates have not been validated for representativeness of Blacks and Whites, however they are commonly used to estimate national estimates of cancer incidence among subgroups in the US. [29,30] Nevertheless,

SEER is a large population based cancer registry with over 35 years of follow-up. It uses a combination of active and passive follow-up to ascertain cancer incidence. Combined with its relatively low rate of race status misclassification in comparison with other cancer registries, SEER is especially appropriate for the study of second primary contralateral breast cancer patho-epidemiological patterns by race.[31,32]

Our results point to the possible bilaterality of many cases of breast cancer. They also suggest shared etiology between cancers in the two contralateral breasts, in many instances as a result of the BRCA1/2 mutations. If this is the case, then this underscores the importance of medical screening, especially since second contralaterals tend to occur within a short time from the diagnosis of the first primary breast cancer.

Our findings may also have relevance for defining the histological criteria for the behavior of in-situ carcinomas of the breast. For instance, we suggest that the primary in-situ lesion diagnosed in women with contralateral breast cancer should be carefully evaluated in order to define the histopathologic criteria for potential malignant behavior, since these in-situ lesions have been associated with a subsequent malignant breast tumor, albeit in the opposite breast, and likely would have progressed if they had not been found.

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Table 1 Clinical and epidemiologic parameters of first and second primary contralateral breast cancer (CBC) by age at diagnosis of the first cancer and race status.

	<45				**≥45**			
	Black n=8,637		**White** n=56,026		**Black** n=31,250		**White** n=35,9638	
	First 1° BC	**Second 1° CBC**	**First 1° BC**	**Second 1° CBC**	**First 1° BC**	**Second 1° CBC**	**First 1° BC**	**Second 1° CBC**
Median nbr of positive lymph nodes	2	3	3	2	3	2	2	2
Tumor Size (mm)	24	20	20	15	20	15	15	14
Median time to second (yrs)	N/A	5.2	N/A	6.41	N/A	4.5	N/A	5.66
Cumulative incidence (at 25 yrs)	N/A	11.8% (10.8-12.9)	N/A	9.9% (9.5-10.3)	N/A	7.7% (7.3-8.2)	N/A	7.3% (7.2-7.5)
Grade								
In Situ	17 (8.5%)	0	150 (15%)	0	139 (23.4%)	0	1,106 (18.7%)	0
Low grade (I,II)	26 (13.0%)	60 (30.0%)	243 (24.3%)	418 (41.8%)	179 (30.1%)	267 (44.9%)	2422 (41.0%)	3486 (59.1%)
High grade (III,IV)	118 (59.0%)	116 (58.0%)	452 (45.2%)	472 (47.2%)	184 (30.9%)	238 (40.0%)	1319 (22.4%)	1563 (26.5%)
Unknown	39 (19.5%)	24 (12%)	155 (15.5%)	110 (11%)	93 (15.6%)	90 (15.1%)	1,054 (17.9%)	852 (14.4%)
ER status								
Borderline	2 (1%)	1 (0.5%)	8 (0.8%)	1 (0.1%)	0	2 (0.3%)	37 (0.6%)	21 (0.4%)
Negative	95 (47.5%)	102 (51%)	348 (34.8%)	338 (33.8%)	134 (22.5%)	183 (30.8%)	873 (14.8%)	1013 (17.2%)
Positive	51 (25.5%)	63 (31.5%)	388 (38.8%)	489 (48.9%)	244 (41%)	310 (52.1%)	3336 (56.5%)	3886 (65.9%)
Unknown	52 (26%)	34 (17%)	256 (25.6%)	172 (17.2%)	217 (36.5%)	100 (16.8%)	1655 (28%)	981 (16.6%)
PR status								
Borderline	1 (0.5%)	2 (1%)	13 (1.3%)	6 (0.6%)	3 (0.5%)	3 (0.5%)	43 (0.7%)	59 (1%)
Negative	96 (48%)	116 (58%)	354 (35.4%)	384 (38.4%)	158 (26.6%)	248 (41.7%)	1162 (19.7%)	1781 (30.2%)
Positive	51 (25.5%)	47 (23.5%)	360 (36%)	422 (42.2%)	211 (35.5%)	236 (39.7%)	2933 (49.7%)	3026 (51.3%)
Unknown	52 (26%)	35 (17.5%)	273 (27.3%)	188 (18.8%)	223 (37.5%)	108 (18.2%)	1763 (29.9%)	1035 (17.5%)

N/A not applicable[1] A test of statistical significance is not provided because it does not account for the competing risk of mortality.

Table 2 Standardized incidence ratios and 95% confidence intervals describing histology of the second contralateral breast cancer by age at diagnosis of the first primary breast cancer, 1973-2007.

	<45			≥45		
Second Ductal[1] after First Ductal[1]	**SIR**	**CI Lower**	**CI Upper**	**SIR**	**CI Lower**	**CI Upper**
White	4.63	4.39	4.89	2.47	2.41	2.53
Black	8.30	7.28	9.43	3.45	3.16	3.76
Second Ductal[1] after First Lobular[2]						
White	2.78	2.32	3.29	2.08	1.96	2.21
Black	3.63	2.03	5.99	2.61	1.99	3.37
Second Lobular[2] after First Lobular[2]						
White	9.94	8.09	12.09	5.75	5.34	6.19
Black	20.00	9.97	35.79	11.38	8.20	15.39
Second Lobular[2] after First Ductal[1]						
White	3.55	3.10	4.05	2.36	2.24	2.48
Black	8.75	6.02	12.29	3.99	3.25	4.85

[1] ICD-O 8500 & 8522
[2] ICD-O 8520

Figure 1 Cumulative incidence of second primary contralateral breast cancers following a first primary breast cancer by age at diagnosis of the first primary breast cancer, 1973-2007.

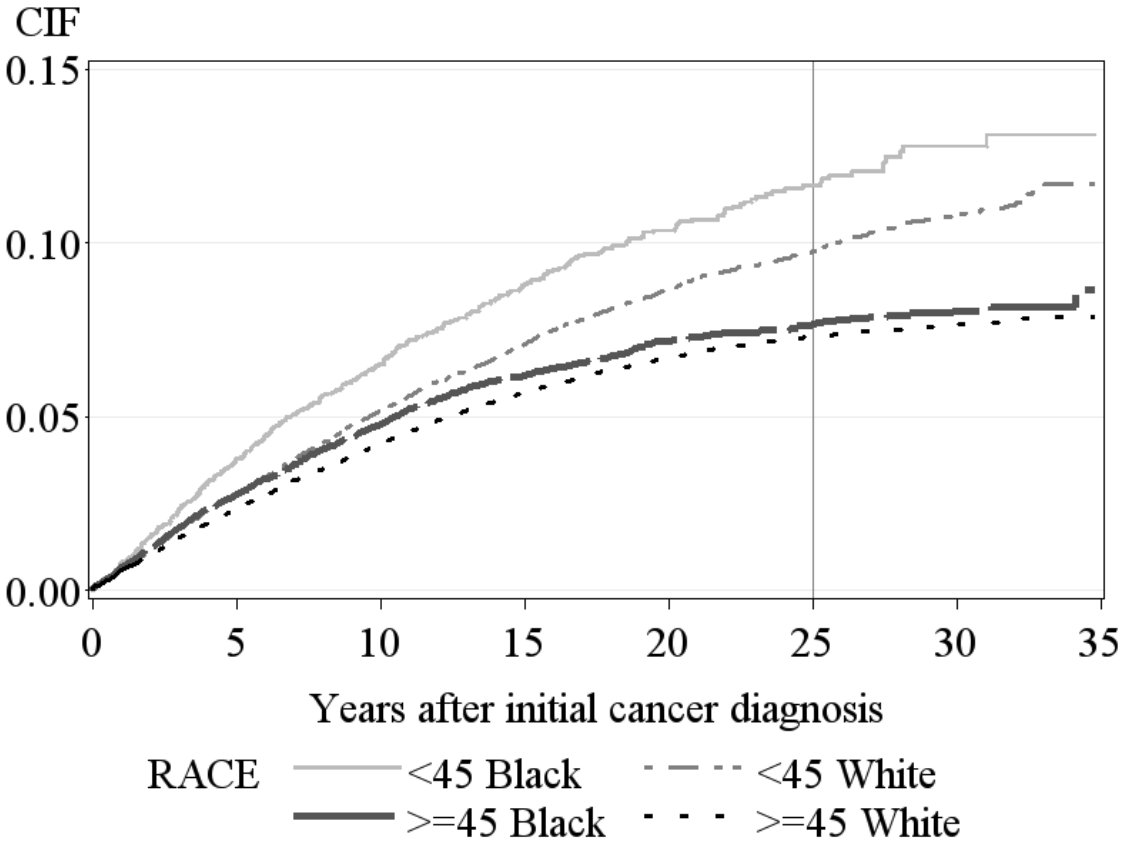


Figure 2 Years between first primary and second primary contralateral breast cancer in Black and White women, 1973-2007.

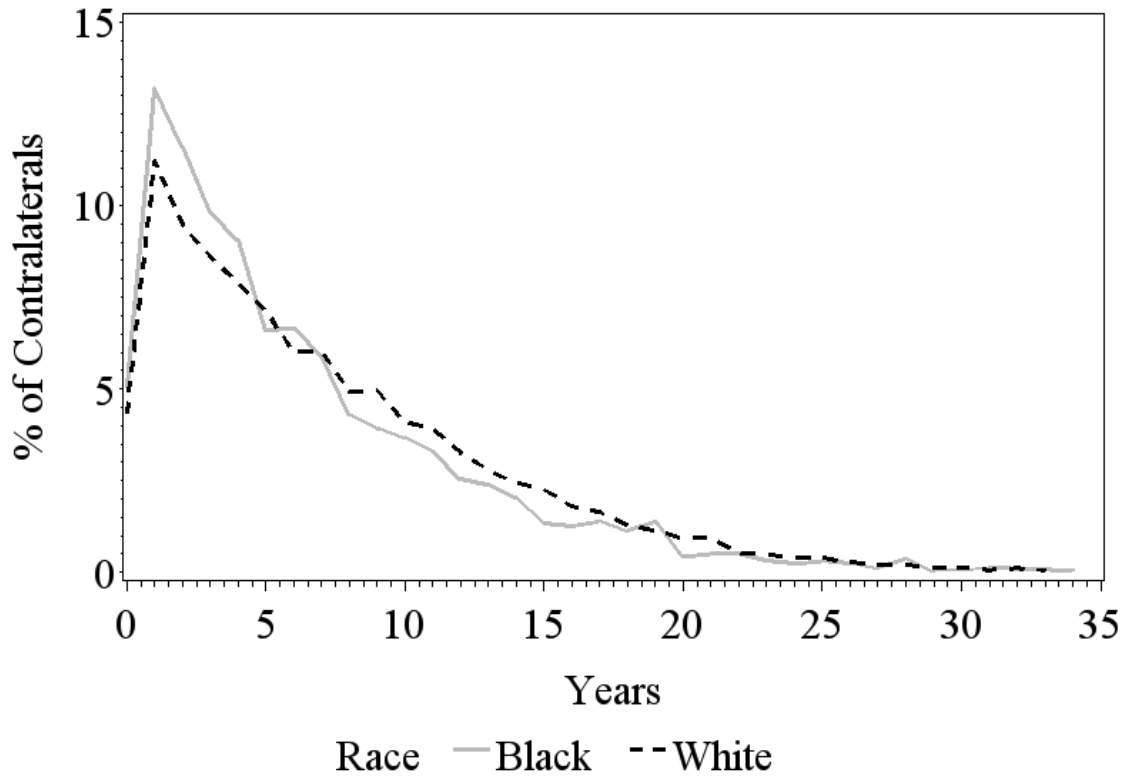
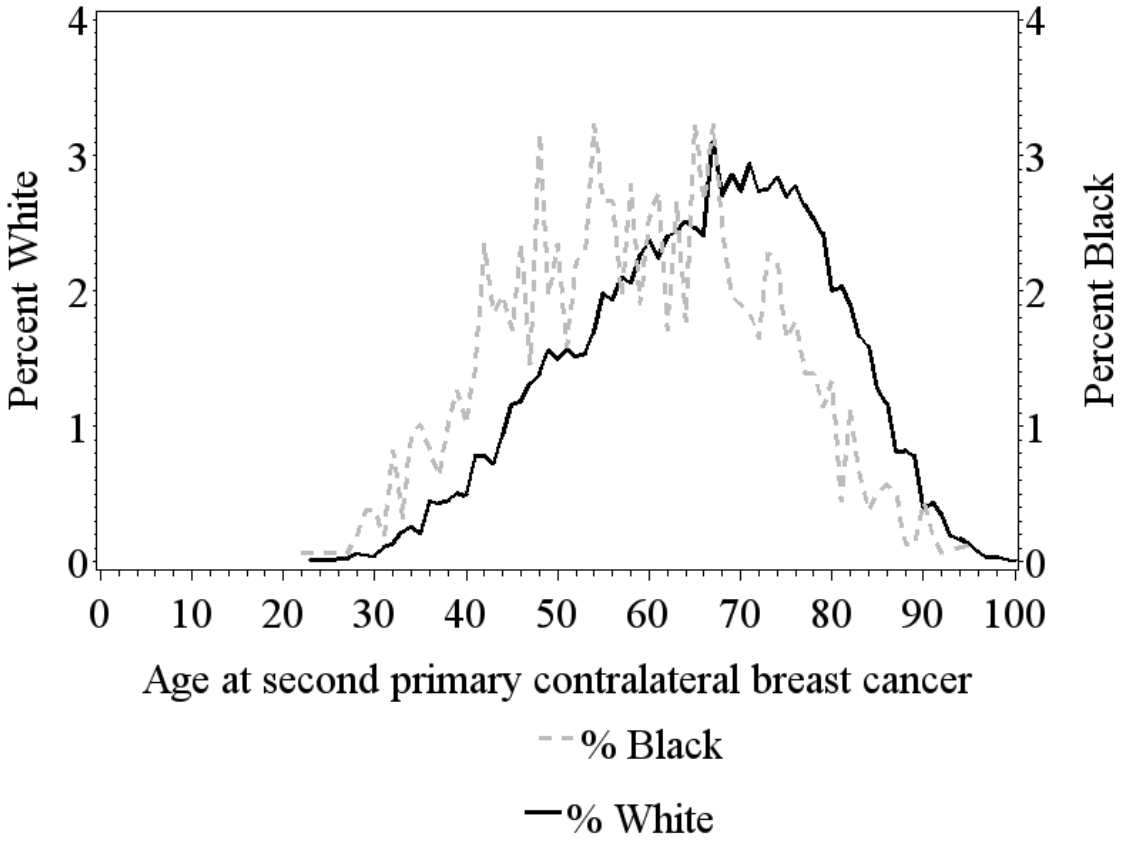


Figure 3 Age distribution of the second primary contralateral breast cancer in White and Black women, 1973-2007.



Chapter 5: Second Primary Colorectal Cancer in Black and White Men and Women

ABSTRACT (Word Count= 298)

BACKGROUND: First primary colorectal cancer (CRC) incidence is higher in men than in women. It has also been decreasing at a higher rate in Whites than in Blacks since the mid-1980s. Despite the differential first primary CRC rates by gender in Blacks and Whites, incidence rates of second primary CRC in Black and White men and women have not been studied. The purpose of this study was to explore the incidence patterns of second primary colorectal cancers in Black and White men and women.

METHODS: SEER's Registry 9 database was used to follow a total of 304,145 female and male, White and Black colorectal cancer survivors, diagnosed at age 19 or older, for the occurrence of a second primary colorectal cancer between 1973 and 2007. Cancers arising in the cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, sigmoid colon, descending colon, rectosigmoid, and rectum qualified as colorectal cancer. Both in situ (15,303; 5.03%) and invasive (273,434; 89.9%) carcinomas were included. Cumulative incidence curves, which account for the competing risks of death and second non-colorectal cancers, were generated; Pepe and Mori's test was used to test for significance.

RESULTS: The incidence of second primary colorectal cancer was significantly higher in men than in women only among patients diagnosed with a first primary colorectal cancer after age 50.

There was no significant difference in the cumulative incidence of second primary colorectal cancers between Blacks and Whites.

CONCLUSION: The incidence patterns of second primary colorectal cancers did not parallel those of first primary colorectal cancers in Black and White men and women. The effect of calendar year on the rates of first primary but not second primary CRC incidence rates suggests that it is unlikely that the differences in CRC incidence between Blacks and Whites would have a purely biological basis.

Keywords: Second colorectal cancer • Age • Race • Gender • Calendar year

INTRODUCTION

Colorectal cancer (CRC) survival at all stages has increased steadily over the past three decades among Black and White men and women in the U.S.[1-3] From the mid-1970s until 2003, the overall 5-year relative survival rate increased from 48.7% to 65.6%.[3] The improvement in survival during this time period was greatest for White males (39.1%) and was comparable among White females and Blacks of both genders (33%).[3] Incidence rates per 100,000 diagnoses of first primary CRC have also steadily decreased since the late 1990s. Between 2000 and 2008, the incidence rates per 100,000 of first primary CRC decreased from 63.7 to 50.4, and from 46.7 to 39.2 in men and women respectively.[3] They remain higher in men than women.[4] Furthermore, while the risk of first primary CRC prior to 1985 was comparable in Blacks and Whites, the incidence rate of first primary CRC has been decreasing at a faster pace in Whites than in Blacks since the mid-1980s.[5] In 2008, the incidence of first primary CRC per 100,000 was 43.4 and 53.4 among Whites and Blacks respectively, in comparison to 67.2 and 63.9 respectively among Whites and Blacks in 1985.[3]

In spite of a steady decline in the overall age-adjusted incidence of primary CRC since the late 1980s, the standardized incidence ratio of second primary CRC has been increasing since the early 1990s.[5,6] A first primary CRC diagnosis between 1988–1992 had a 1.18 (95% CI 1.06–1.31) higher relative hazard of a second CRC than a comparable first primary CRC diagnosed between 1973–1977.[6] CRC survivors are at a 1.4 (95% CI 1.3–1.4) to 1.6 (95% CI=1.1–2.2) higher risk of a second primary CRC than the general population.[6,7] Yet the incidence of second primary CRC in Black and White men and women has not been investigated. The purpose of this study was to determine the incidence patterns of second primary colorectal cancers in Black and White men and women. By comparing the incidence patterns of first and second primary CRC

among Black and White men and women, the findings may reveal clues about the pathogenesis of colorectal cancer.

SUBJECTS AND METHODS

Study Population

The SEER's Registry 9 database was used to follow a total of 304,145 female (151,572; 49.84%) and male (152,573; 50.16%), White (276,952; 91.06%) and Black (27,193; 8.94%) colorectal cancer survivors, diagnosed at age 19 or older, for the occurrence of a second primary colorectal cancer between 1973 and 2007. SEER's registry 9 covers 8.8% and 9.0% respectively of the Black and White populations. Chosen for their epidemiologically significant population subgroups, SEER regions are reasonably representative of the racial diversity of the US.[8] SEER determines racial identity using a combination of medical records, physician and nursing notes, photographs, and any other available sources. According to SEER, a second primary cancer was defined as one that arises independently in a new anatomic site or tissue at least two months subsequent to the diagnosis of the first primary cancer, or arises in the same primary anatomic site but has a histopathology different from the first primary cancer.[9] Cancers arising in the cecum, ascending colon, hepatic flexure, transverse colon, splenic flexure, sigmoid colon, descending colon, rectosigmoid, or rectum qualified as colorectal cancer.

Statistical Methods

Data were compiled using SEER*Stat's Multiple Primary -- Standardized Incidence Ratios (MP-SIR) session and imported into SAS. They were stratified by age 50 years as a surrogate for hereditary and familial cases which tend to occur at younger ages as well as menopause in

women.[10,11] Cumulative Incidence Function (CIF) curves, which account for competing events, were generated to describe, among first primary colorectal cancer survivors, the probability of developing a second primary colorectal cancer.[12] Pepe and Mori's test, which is a two-sample test of the equality of two CIFS, was used to test for significant differences in cumulative incidence of second primary cancers by gender and between Blacks and Whites.[13] Subjects were censored at the date last known to be alive (3,866; 1.3%) or SEER follow-up cutoff date of December 31, 2007 (77,734; 25.6%), whichever came first. Death (185,973; 61.1%) and the occurrence of non-colorectal second primary cancers (29,440; 9.7%) were treated as competing events. SEER*Stat 6.2.2 and SAS 9.2 were used for all analyses.

RESULTS

A total of 7,132 second primary colorectal cancers were observed among 299,096 patients who had survived 2 months or more after a first primary colorectal cancer diagnosed between 1973-2007. Among first primary colorectal cancer survivors, 2.3% (607) of Blacks and 2.4% (6,525) of Whites developed a second colorectal cancer. The majority of first primary colorectal cancer patients (276,448; 90.9%) were diagnosed after age 50.

The median interval in years between the first and second primary colorectal cancers was shorter among patients diagnosed with a first primary colorectal cancer after age 50. Females diagnosed at age 50 or earlier had shorter median times to the second primary colorectal cancer than males; there was no difference by gender among first primary colorectal cancer patients diagnosed after age 50. Blacks had shorter median times to the second primary colorectal cancer than Whites at any age of diagnosis (Table 1).

Differences by Gender

Second primary colorectal cancer incidence rates among CRC patients diagnosed in 1985 or later were significantly higher than the respective rate across the study period ($p<0.05$). Results are therefore presented for first primary CRC patients diagnosed in 1985 or later. The cumulative incidence of second primary colorectal cancer was significantly higher in men than in women among patients diagnosed with a first primary colorectal cancer after age 50 ($p=0.004$). No significant difference was however observed between men and women among patients diagnosed with the first primary colorectal cancer at age 50 or earlier. Compared to patients diagnosed with the first primary colorectal cancer at age 50 or earlier, the cumulative incidence of second primary colorectal cancer was higher among both men and women diagnosed with the first primary colorectal cancer after age 50 (Figure 1).

Differences by Race

Compared to 1973-1984 (Figure 2), the difference in cumulative incidence of second primary colorectal cancer between Blacks and Whites widened starting in the mid-1980s (Figure 3). Nevertheless, the difference in the cumulative incidence of second primary colorectal cancer between Blacks and Whites was not significant independent of the age at diagnosis of the first primary colorectal cancer. The cumulative incidence of second primary colorectal cancer among colorectal cancer survivors is presented in Table 2.

DISCUSSION

This study has compared the cumulative incidence of second primary colorectal cancer in Black and White men and women among colorectal cancer survivors over 35 years.

Consistent with first primary colorectal cancer rates, men had a significantly higher incidence of second primary colorectal cancer than women in patients diagnosed with a first primary colorectal cancer after age 50.[4,5] While men also had a higher incidence of second primary colorectal cancer than women diagnosed with a first primary colorectal cancer at age 50 or earlier, the difference was not statistically significant. It has been proposed that estrogen present in pre-menopausal women preferentially protects against microsatellite unstable cancers and therefore contributes to the colorectal cancer disparity observed between men and women before age 50.[14] Hormone replacement therapy which is started at the time of menopause around age 50 has been associated with a decreased risk of colorectal cancer.[15-17] Further, the prevalence of the P53 mutation associated with colorectal cancer has been found to increase with age in men, and to decrease with age in women.[16] It therefore appears that a combination of genetic factors and hormone supplementation may be implicated in the significant second primary colorectal cancer incidence gender disparity after age 50.

Second primary CRC cumulative incidence rates did not differ between Blacks and Whites independent of the age at diagnosis of the first primary CRC. This pattern does not parallel earlier findings of an emerging widening gap in the incidence of first primary CRC between

Blacks and Whites, which has been attributed to widespread screening following President Reagan's colorectal cancer diagnosis in 1985.[5,18] In addition, while it is estimated that approximately 5% of colorectal cancer patients have a positive family history, there is no evidence of a differential distribution of family history between Blacks and Whites.[19] It therefore is unlikely that the disparity in colorectal cancer rates between Blacks and Whites would have a purely biological basis.

Across genders in Blacks and Whites, the incidence of second primary colorectal cancer increased with older age. This observation parallels a similar pattern seen in first primary colorectal cancer and is in keeping with the theory of a linear age-specific long-term multistep adenoma-to-carcinoma sequence.[20-22]

This study has limitations typical of a descriptive epidemiologic study using the SEER database. The accuracy of the second cancer incidence rates are dependent on SEER's coding rules for multiple primaries. Other organizations such as the International Association for Cancer Registries (IACR) have different definitions which may not be congruent with SEER's definition.[23] Consequently, analyses using different definitions may yield dissimilar results. The interpretation of the incidence estimates is potentially impacted by the limited treatment information available in SEER which affects survival and consequently the incidence of seconds. They could also be underestimated as a result of SEER population mobility. While our results were stratified by age, we did not test for an age by race interaction due to the size of the SEER dataset and limitations in computing resources. As the only national cancer registry in the US, SEER incidence rates have not been validated for representativeness of Blacks and Whites,

however they are commonly used to estimate national estimates of cancer incidence among subgroups in the US.[24,25] Nevertheless, SEER is a large population based cancer registry with over 35 years of follow-up. It uses a combination of active and passive follow-up to ascertain cancer incidence. Combined with its relatively low rate of race status misclassification in comparison with other cancer registries, SEER is especially appropriate for the study of second primary incidence trends by race following a first primary colorectal cancer second cancer incidence rates by race.[26,27]

Consistent with a linear age-specific long-term multistep adenoma-to-carcinoma sequence, the incidence pattern of second primary colorectal cancer parallel those of first primary colorectal cancers. The emergence of first primary CRC incidence rate differences between Blacks and Whites starting in the mid-1980s combined with the absence of disparities in second primary CRC incidence rates suggests that it is unlikely that the differences in CRC rates between Blacks and Whites would have a purely biological basis. This underscores the importance of intensifying CRC screening efforts among Blacks to bridge the CRC incidence disparity and alleviate its burden.

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Tables

Table 1 Median interval in years between the first and second primary colorectal cancers, by gender, race and age at diagnosis of the first primary colorectal cancer.

	≤50	**>50**
Females[1]	5.0	4.0
Males[1]	6.1	4.0
Blacks[1]	4.7	3.5
Whites[1]	5.8	4.0

*A test of statistical significance is not provided because it does not appropriately account for mortality.
[1] Restricted to second primary colorectal cancers following first primary colorectal cancer diagnosed 1985+.

Table 2 Cumulative incidence of second primary colorectal cancer 25 years after the first primary colorectal cancer, by age at diagnosis of the first primary colorectal cancer.

	1st Primary Colorectal Cancer ≤50	**1st Primary Colorectal Cancer >50**
Sex		
Female[1,2]	1.2% (1.0 – 1.5)	2.0% (2.0 - 2.2)
Male[1,2]	1.7% (1.4 – 2.0)	2.2% (2.1 – 2.3)
Race		
Black[1,2]	1.9% (1.5 – 2.6)	2.3% (2.0 – 2.5)
White[1,2]	1.4% (1.2 – 1.6)	2.1 % (2.0 – 2.2)

[1] Restricted to second primary colorectal cancers following first primary colorectal cancer diagnosed 1985+.
[2] 10 years following the first primary colorectal cancer diagnosis.

Figure 1 Cumulative incidence of second primary colorectal cancer among men and women diagnosed with a first primary colorectal cancer in 1985 or later, by age at diagnosis of the first primary colorectal cancer.

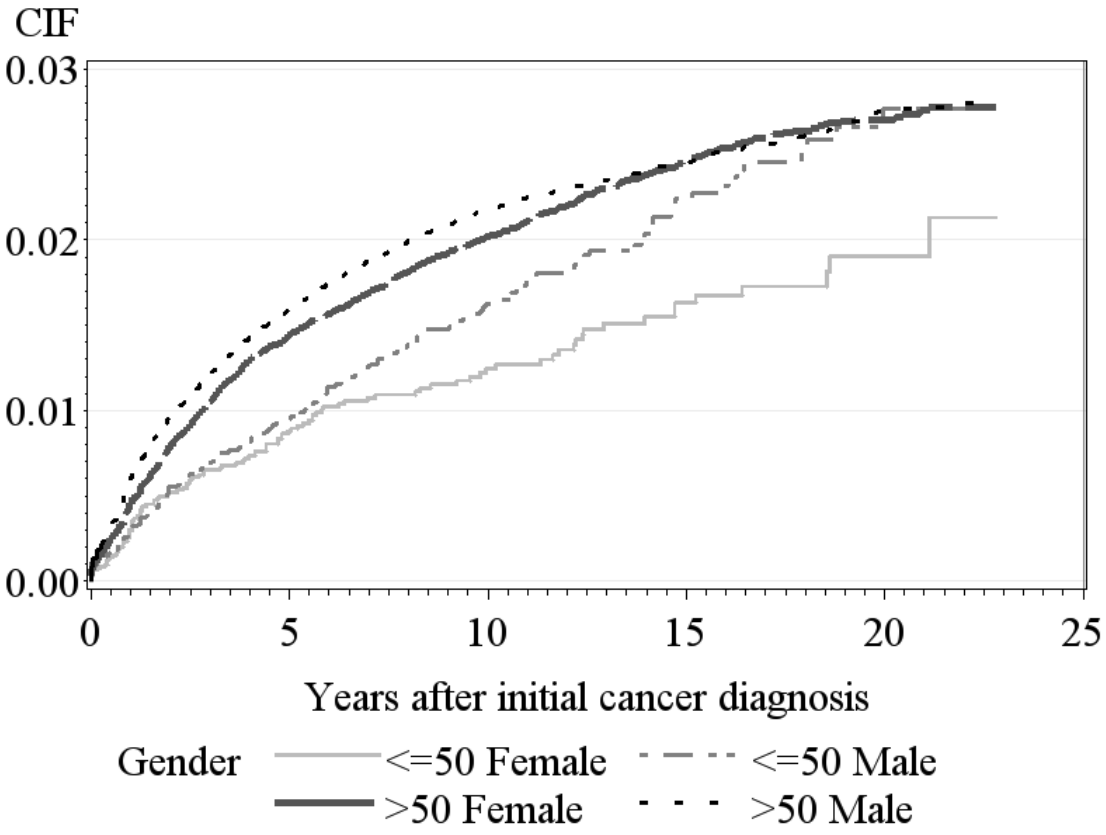


Figure 2 Cumulative incidence of second primary colorectal cancer in Blacks and Whites diagnosed with a first primary colorectal cancer before or after age 50, 1973-1984.

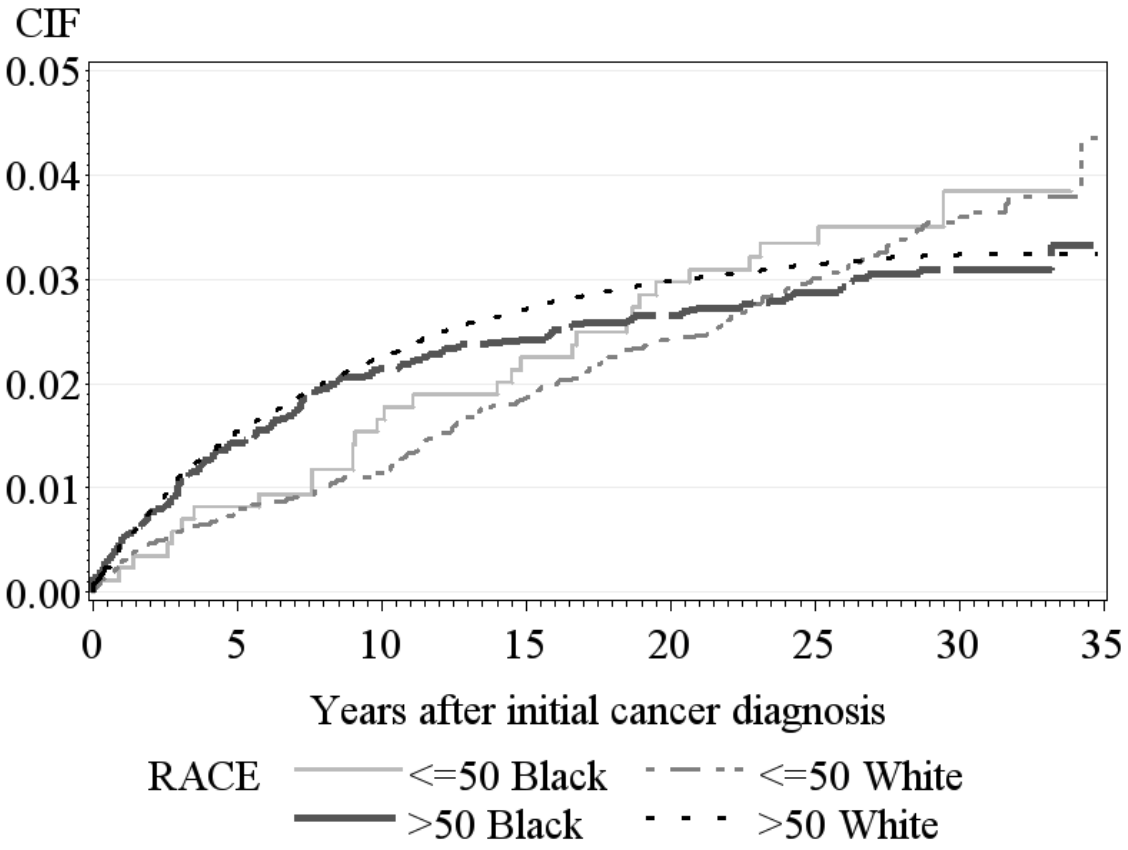
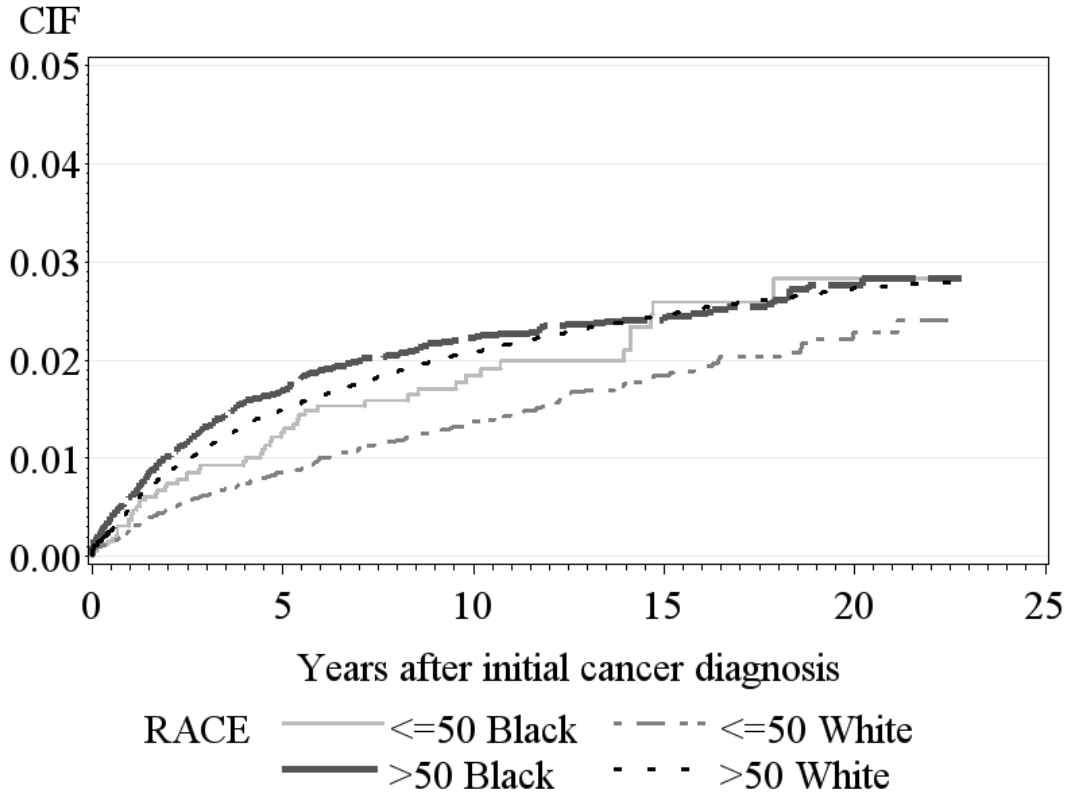


Figure 3 Cumulative incidence of second primary colorectal cancer in Blacks and Whites diagnosed with a first primary colorectal cancer before or after age 50, 1985-2007.



Chapter 6: Conclusions

This dissertation contributes to the scarce literature examining the incidence of second primary cancers among Blacks and Whites in the Unites States. It was undertaken to determine whether a first primary breast or colorectal cancer in Blacks places them at a higher risk for developing a second primary cancer than a comparable first primary cancer in Whites. Two general approaches were adopted:

By comparing incidence patterns of first and second primary cancers, we were able to contribute to the understanding of disparities between Blacks and Whites. It was counter-intuitive that we found that second primary cancer incidence rates in Blacks and Whites did not necessarily follow the pattern of the first primary cancer, or that of a first primary cancer of the same anatomic site. We found, for example, that the incidence of second primary breast cancers was higher among Blacks than Whites, independent of the age at diagnosis of the first primary breast cancer. This is in contrast to the incidence of first primary breast cancer which is higher among Black women diagnosed before age 45, but higher among White women diagnosed after age 45.[1] This observation seems to reflect a number of possibilities that in general are difficult to resolve. It is possible that Blacks have higher rates of second primary cancers than Whites in the ipsilateral breast, although some of these cancers may be recurrences. It may be that Blacks are truly more prone to second primary cancers in the ipsilateral and contralateral breasts. It is also possible that Blacks may be more prone to bilateral breast cancer with the contralateral cancer presenting later that the first cancer. Nonetheless, it seems unusual that Blacks who have a lower

incidence of post menopausal breast cancer than Whites have a higher rate of second primary breast cancers than Whites in the post menopausal period and merits further study.

In contrast to this, we found that the incidence patterns of second primary gynecologic cancers in breast cancer survivors paralleled those of the first primary cancers in the respective anatomic sites. The incidence of endometrial second primary cancers was significantly higher among White than Black women, regardless of age at diagnosis of the first breast cancer. This is opposite of the pattern seen for first primary breast cancer but is consistent with the reported lower incidence of first primary gynecologic cancers among Blacks compared with Whites.[2] This observation may be a reflection of the higher rates of hysterectomies for benign conditions among Blacks, which precludes the development of a second primary endometrial cancer and therefore artifactually contributes to their lower second primary endometrial cumulative incidence rates in comparison to Whites.[3-5] Furthermore, Tamoxifen (Nolvadex®) which has been implicated in the development of second primary endometrial cancers in breast cancer survivors is more commonly used for the treatment of regional-stage disease in Whites than Blacks. [6-8] It is possible that the difference in Tamoxifen treatment between the two groups, likely resulting from the higher prevalence of ER+ breast cancers in Whites than Blacks, contributes to the higher cumulative incidence of second endometrial primaries among White compared with Black women. The extent of this contribution is however expected to be limited because of the low absolute risk of Tamoxifen-related second primary endometrial cancer.

Second primary ovarian cancers were also significantly more common among White than Black women, regardless of the age at diagnosis of the first primary breast cancer. This is consistent with previous reports of a higher incidence of second ovarian cancers among White compared with

Black breast cancer survivors, and parallels the reported lower incidence of first primary gynecologic cancers among Blacks compared with Whites.[2,9] The prevalence of BRCA1, which is associated with an increased risk of breast and ovarian cancers, is higher in White than in Black women. It is possible that the increased incidence of ovarian cancer could be in part a reflection of the higher prevalence of BRCA1.[10]

It was also counter-intuitive that we found that second primary colorectal cancer incidence rates in Blacks and Whites did not entirely follow the pattern of the first primary colorectal cancer. For example, we did not find significant differences in the incidence of second primary colorectal cancers between Blacks and Whites despite higher first primary colorectal cancer incidence in Blacks than Whites since the mid-1980s that is largely attributed to widespread screening following President Reagan's colorectal cancer diagnosis in 1985.[11,12] The emergence of first primary CRC incidence rate differences between Blacks and Whites starting in the mid-1980s, combined with the absence of disparities in second primary CRC incidence rates, suggests that it is unlikely that the differences in CRC rates between Blacks and Whites has a purely biological basis. Consistent with first primary colorectal cancer rates, men had a significantly higher incidence of second primary colorectal cancer than women in patients diagnosed with a first primary colorectal cancer after age 50.[11,13] While men also had a higher incidence of second primary colorectal cancer than women diagnosed with a first primary colorectal cancer at age 50 or earlier, the difference was not statistically significant. It has been proposed that estrogen present in pre-menopausal women preferentially protects against microsatellite unstable cancers and therefore contributes to the colorectal cancer disparity observed between men and women before age 50.[14] Hormone replacement therapy, which is typically started at the time of menopause, around age 50, has been

associated with a decreased risk of colorectal cancer.[15-17] Further, the prevalence of the P53 mutation associated with colorectal cancer has been found to increase with age in men, and to decrease with age in women.[18] It therefore appears that a combination of genetic factors and hormone supplementation may be implicated in the significant second primary colorectal cancer incidence gender disparity after age 50. Among Black and White men and women, the incidence rates of second primary colorectal cancer increased with age, lending further support to the theory of a linear age-specific long-term multistep adenoma-to-carcinoma sequence.[18,19]

By comparing the clinical and demographic parameters of second primary cancers in Blacks and Whites to those of the first primary cancer, we were able to make general observations about cancer pathogenesis. For example, we found that second primary contralateral breast cancers presented at an earlier age in Blacks, and were more likely to be larger, less differentiated, and had a comparable numbers of lymph nodes as Whites. Comparing the first primary and second contralateral breast cancers, we found that the likelihood of concordant histology in ductal or lobular breast cancer was higher than discordant occurrence. Ductal second primary contralateral breast cancers were more likely preceded by a first primary ductal than lobular breast cancer; the same was true for breast cancers of a lobular histology. This observation interestingly also applied to women diagnosed with a first primary lobular breast cancer, despite the decreasing rate of lobular breast cancer in women ages 45 years and older. ER status of the first and second primary contralateral breast cancers was also more likely to be congruent among both Black and White women. In combination, our results lend preliminary support to the bilaterality of many cases of breast cancer, and to shared etiology between cancers in the two contralateral breasts.

Strengths and Limitations

This dissertation has limitations typical of a descriptive epidemiologic study using the SEER database. The accuracy of the second cancer incidence rates is dependent on the definition used by SEER for multiple primary cancers.[20] Other organizations such as the International Association for Cancer Registries (IACR) have different definitions, which are not congruent with SEER's definition.[21] For instance, IACR does not take the lapse between cancer diagnoses into account and considers all cancers occurring in bilateral organs as one primary. Consequently, analyses using different second primary cancer definitions will yield dissimilar results. SEER only documents the cancer incidence experience of patients residing in designated geographic areas. The incidence of second primary cancers could therefore be underestimated as a result of population mobility in the SEER catchment areas. SEER uses a combination of active and passive follow-up, however the specific definition of what constitutes each varies by registry. For instance, while certain registries, such as the San-Jose registry, carry out direct patient contact as part of their active follow-up, other registries, such as the Los Angeles registry, do not initiate any patient contact in their active follow-up. The variation in data collection techniques is likely to affect the quality of the SEER follow-up data. SEER also collects information on only the first course of cancer treatment for all diagnosed cancers; this includes surgery, radiation, hormonal therapy, chemotherapy, and immunotherapy. However due to cost and accuracy considerations, only information on surgery and radiation are included on the SEER public-use files. The interpretation of incidence estimates may be, as a result, affected by the limited treatment information available in SEER which affects survival and consequently the incidence of second primary tumors. To decrease the potential for misclassification, racial identity in SEER was determined using a combination of medical records,

physician and nursing notes, photographs, and any other available sources. As the only national cancer registry in the US, SEER incidence rates have not been validated for representativeness of Blacks and Whites, however they are commonly used to estimate national estimates of cancer incidence among subgroups in the US.[22,23] Nevertheless, SEER is a large population based cancer registry with over 35 years of follow-up. It uses a combination of active and passive follow-up to ascertain cancer incidence. Combined with its relatively low rate of race status misclassification and non-bias ascertainment in comparison with other cancer registries, SEER is especially appropriate for the study of second cancer incidence rates by race.[24,25]

Future Directions

Our results have furthered the understanding of cancer disparities among first primary breast and colorectum cancers and select second primary cancer following them. They have also contributed to the understanding of breast and colorectal cancer pathogenesis. Future research could expand on our findings in a number of ways. It is only recently that that SEER dataset has grown to a size that allows the study of second cancer incidence among population subgroups. This research project is the first investigation to our knowledge of second primary cancer incidence rates in Blacks and Whites. It is therefore appropriate that our results be confirmed using databases other than SEER. As SEER further matures, the study of second and subsequent primary cancer incidence patterns in additional anatomic sites and in less common minority groups such as Hispanics will become possible and may further our insight into cancer pathogenesis and disparities. Furthermore, as the software and computing resources develop, it will become possible

to re-examine cumulative incidence of second primary cancers accounting for relevant clinical characteristics such as stage.

The SEER database does not collect many of the known cancer risk factors and hence often does not support the study of cancer etiology. It is possible that the suspected risk factors thought to precipitate the differences in first primary incidence rates between Blacks and Whites may be implicated in part in the differences in second primary cancer incidence rates between Blacks and Whites. Cancer data sources that collect this information may be instrumental in determining the commonality between risk factors for the first and second primary cancers which may further broaden the understanding of breast cancer etiology differences between Blacks and Whites.

This dissertation has established a successful framework for the study of second primary cancer incidence. Our results contribute to the understanding of cancer disparities between Blacks and Whites by comparing incidence patterns of first and second primary cancers. Our results also expand the current understanding of cancer pathogenesis by comparing the clinical parameters of second primary cancers between Blacks and Whites to those of the first primary cancer. In summary, future research should focus on expanding the application of our framework to other cancer sites and population subgroups. National data collection efforts should focus on collecting suspected risk factors concomitantly with cancer outcomes. Developing a better understanding of second primary cancer risk is necessary to guiding the long-term management of the burgeoning population of cancer survivors. It may also be a required step in the transformation of cancer to a manageable illness.

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Appendix

Presented below are results of analyses that were not chosen for any of the three papers.

Table 1 Age-adjusted incidence rates for first primary breast, colorectal, thyroid cancers, SEER 9, 1973-2006. [In support of papers 1, 2, & 3]

		Breast[1,2,3,4]	Colorectal[1,2,3,4]	Thyroid[1,2,3]
White	**Female**	163.42	51.00	16.60
Black	**Female**	148.60	65.89	8.43
White	**Male**	N/A	65.03	5.66
Black	**Male**	N/A	77.90	2.34

[1] Rates per 100,000, for 2006
[2] Age-adjusted using 2000 single age standard populations
[3] Pop'ns adjusted for subjects not at risk of getting first cancer (i.e. already had first – prevalent)
[4] Excludes childhood cancers ages <19

Table 2 Age-adjusted incidence rates for second primary cancers following first primary breast cancer, by cancer site, SEER 9, 1973-2006. [In support of paper 1 & 2]

		Any Site[1,2,3]	Any Site Excpt Breast[1,2,3]	Lung and Bronchus[1,2,3]	Corpus Uteri[1,2,3]	Ovary[1,2,3]
White	**Female**	884.71	438.82	78.35	56.17	28.56
Black	**Female**	1177.39	409.47	82.35	32.03	16.64

[1] Rates per 100,000, for 2006
[2] Age-adjusted using 2000 single age standard populations
[3] Excludes childhood cancers ages <19

Table 3 Age-adjusted incidence rates for second primary cancers following first primary colorectal cancer, by cancer site, SEER 9, 1973-2006. [In support of paper 3]

		Any Site[1,2,3]	Any Site Excpt Colorectal[1,2,3]	Breast[1,2,3]	Prostate[1,2,3]	Lung and Bronchus[1,2,3]	Colorectal[1,2,3]
White	**Female**	796.10	781.80	163.66	N/A	126.93	14.31
Black	**Female**	541.44	508.48	182.37	N/A	67.41	32.95
White	**Male**	1091.42	1046.77	N/A	306.61	80.75	44.64
Black	**Male**	991.05	789.40	N/A	274.93	180.29	201.65

[1] Rates per 100,000, for 2006

[2] Age-adjusted using 2000 single age standard populations
[3] Excludes childhood cancers ages <19

Table 4 Age-adjusted incidence rates for second primary cancers following first primary thyroid cancer, by cancer site, SEER 9, 1973-2006. [Cancer site dropped]

		Any Site[1,2,3]	Any Site Excpt Thryoid[1,2,3]	Breast[1,2,3]	Prostate[1,2,3]	Lung and Bronchus[1,2,3]	Thyroid[1,2,3]
White	**Female**	0.00425	0.00411	0.00164	N/A	0.00051	0.00014
Black	**Female**	0.00509	0.00031	0.00228	N/A	0.00198	0.00000
White	**Male**	0.00522	0.00507	N/A	0.00202	0.00033	0.00015
Black	**Male**	0.01138	0.01138	N/A	0.00662	0.00148	0.00000

[1] Rates per 100,000, for 2006
[2] Age-adjusted using 2000 single age standard populations
[3] Excludes childhood cancers ages <19

Table 5 Crude incidence rates using Poisson regression for second primary cancers following first primary breast cancer, by cancer site, SEER 9, 2007. [In support of papers 1 & 2]

	Any Site[1,2]	Breast[1,2]	Lung and Bronchus[1,2]	Corpus Uteri[1,2]	Ovary[1,2]
White	1540	630	200	80	50
Black	1660	820	160	100	30
Black Vs White	1.08 (0.96 - 1.21)	1.31 (1.1 - 1.55)	0.8 (0.55 - 1.16)	1.17 (0.72 - 1.91)	0.55 (0.22 - 1.35)
P-value	0.2193	0.0019	0.2445	0.5169	0.1959

[1] Crude rates per 100,000, for 2007
[2] Excludes males, childhood cancers ages <19

Table 6 Age-adjusted incidence rates using Poisson regression for second primary cancers following first primary breast cancer, by cancer site, SEER 9, 2007. [In support of papers 1 & 2]

	Any Site[1,2]	**Breast**[1,2]	**Lung and Bronchus**[1,2]	**Corpus Uteri**[1,2]	**Ovary**[1,2]
White	440	200	2.25	Model did not converge.	0.72
Black	510	260	2.11803	Model did not converge.	0.409
Black Vs White	1.16 (1.03 - 1.31)	1.29 (1.08 - 1.53)	0.94 (0.64 - 1.37)	Model did not converge.	0.56 (0.23 - 1.39)
P-value	0.0139	0.0037	0.7572	Model did not converge.	0.2149

[1] Age-adjusted crude rates per 100,000, for 2007
[2] Excludes males, childhood cancers ages <19

Figure 1 Conditional probability of any second primary cancer among Black and White women diagnosed with a first primary breast cancer before age 45, or at age 45 or older, 1973-2007. [In support of paper 1]

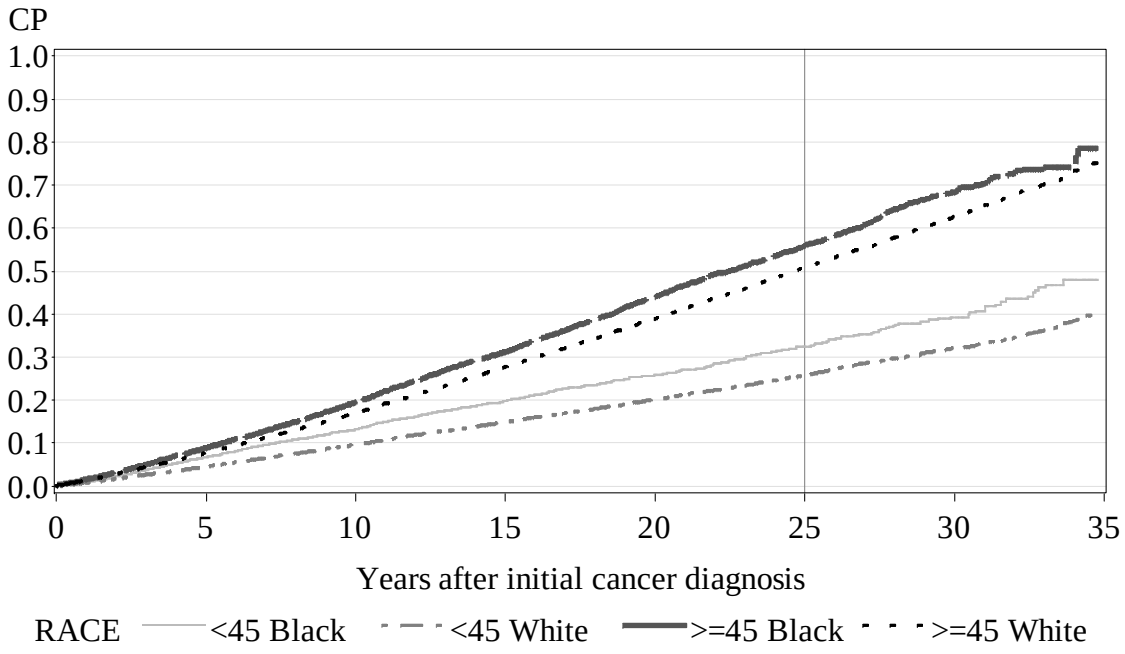


Figure 2 Conditional probability of second primary breast cancer among Black and White women diagnosed with a first primary breast cancer before age 45, or at age 45 or older, 1973-2007. [In support of paper 1 & 2]

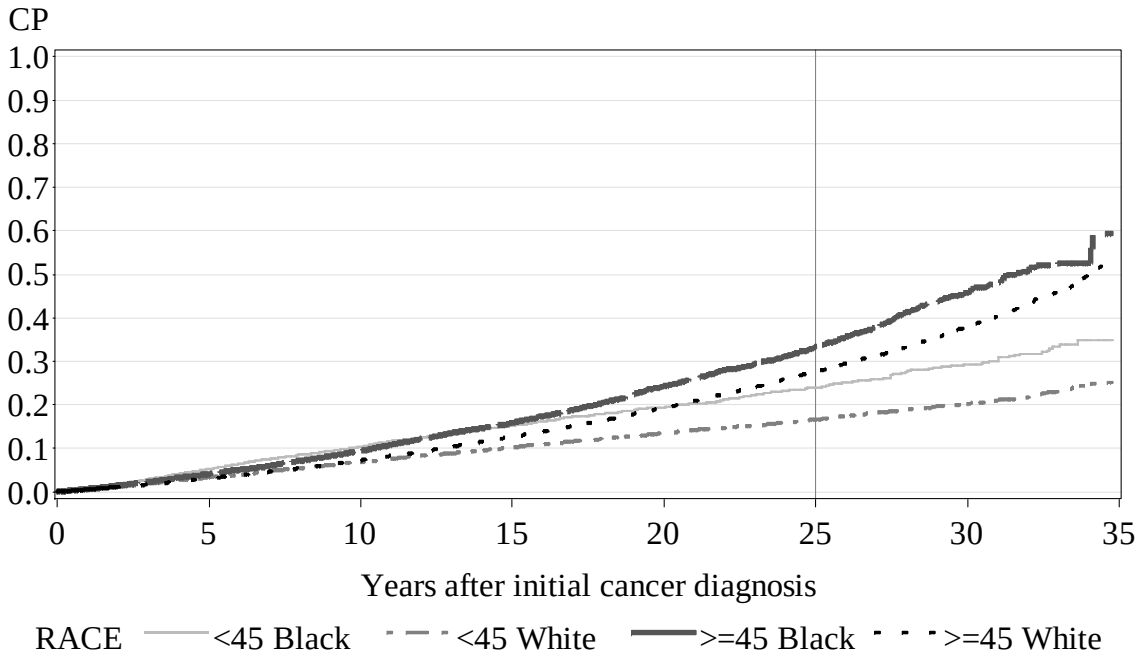


Figure 3 Conditional probability of second primary endometrial cancer among Black and White women diagnosed with a first primary breast cancer before age 45, or at age 45 or older, 1973-2007. [In support of paper 1]

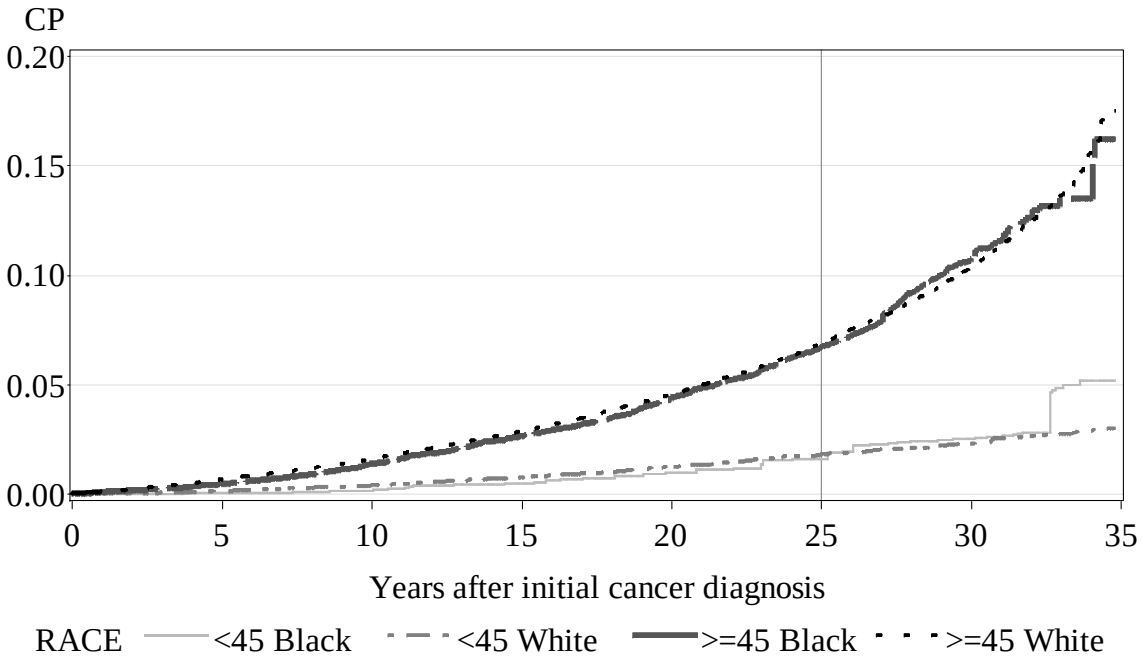
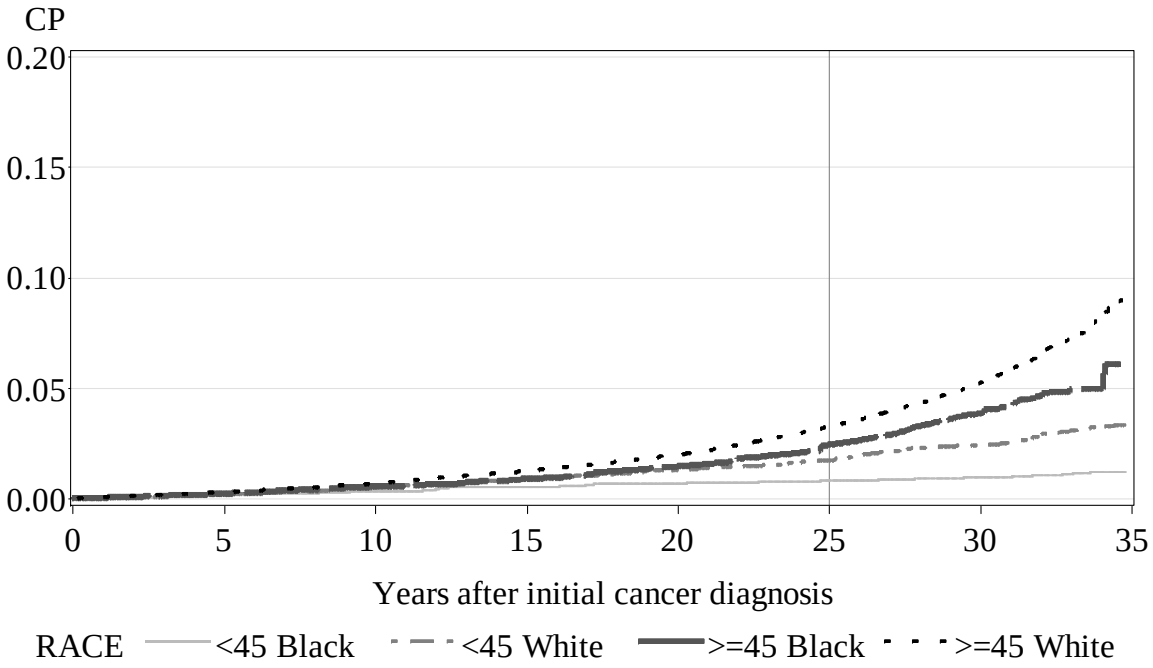


Figure 4 Conditional probability of second primary ovarian cancer among Black and White women diagnosed with a first primary breast cancer before age 45, or at age 45 or older, 1973-2007. [In support of paper 1]



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