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Report

Racial and age differences in multiple primary cancers after breast cancer: A population-based analysis

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Summary

The occurrence of multiple primary cancers was evaluated among 17,944 white and black female residents of Metropolitan Detroit diagnosed with breast cancer between 1973 and 1983. Invasive second primary cancers were diagnosed among 1106 of these women, almost twice the expected number. Subsequent *in situ* cancers were detected four times more often than expected. Fifty-six percent of the subsequent invasive cancers were of the breast (Standardized Incidence Ratio, SIR = 3.80). Black women experienced higher risk of subsequent breast cancers (SIR = 5.30) than white women (SIR = 3.62). Highest risk was seen among women first diagnosed before age 40 (SIR for black women = 26.15, SIR for white women = 10.87) and within five years of initial diagnosis. These findings suggest that young breast cancer patients, especially black women, are at high risk of developing a second primary breast cancer soon after their initial diagnosis and should be under continued medical surveillance. The occurrence of multiple primary breast cancers among young women suggests a genetic component to risk. Identification of this subpopulation would be useful in the study of molecular and genetic markers for cancer. Subsequent colon (SIR = 1.24) and cervical (SIR = 1.54) cancers also were diagnosed significantly more often than expected, as were ovarian cancers among white women (SIR = 1.45). These findings are consistent with common etiologic factors associated with these cancers.

Introduction

A number of studies have described the occurrence of multiple primary cancers in women diagnosed with first primary breast cancer [1–7]. While earlier investigations focused on clinical case reports and autopsy series [8], more recent work has involved population-based cancer registries in a cohort approach [4–7]. This type of investigation has several advantages, including the availability of incidence rates for the study population from which one can determine expected risk, the ability to provide complete follow-up of the population over time, the large number of cases, and the ability to describe population risks among blacks and whites in different age groups. The study of multiple cancers has been valuable in suggesting etiologic mechanisms for the occurrence of certain cancers. The presence of multiple cancers in an individual might suggest risk factors common to both cancers, individual susceptibility to cancer, or treatment-induced disease. By identifying those cancer patients

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at highest risk of developing multiple cancers, early detection efforts can be directed to the most appropriate groups, as can studies of molecular and genetic markers of cancer risk.

The aim of the present investigation was to determine if there was excess risk of multiple cancers among black and white women first diagnosed with breast cancer in Metropolitan Detroit. Risk of multiple primary cancers among black women has never been evaluated using a population-based sample. Risk also was evaluated by age at diagnosis of the first breast cancer and by length of follow-up after first diagnosis.

Methods

Between 1973 and 1983, 17,944 invasive, microscopically confirmed, first primary breast cancers were diagnosed among white and black female residents of Metropolitan Detroit. These women were identified through the Metropolitan Detroit Cancer Surveillance System (MDCSS), a participant in the National Cancer Institute's Surveillance, Epidemiology, and End Results (SEER) program. The cohort was followed as part of routine annual follow-up procedures, which include contact with physicians' offices, review of hospital medical records, and direct patient contact. Approximately 95% of the MDCSS cancer patients have current (within the last year) follow-up, thus reducing the likelihood of surveillance bias. Reports of subsequent cancer occurrences were reviewed, according to SEER guidelines, to determine if subsequent cancers were due to metastatic or recurrent disease or new primary cancers. These criteria include an evaluation of histologic types, dates of diagnosis, and sites within the body. Comprehensive quality control reviews are performed on an annual basis by senior abstracting staff as well as by members of the national SEER staff. This procedure entails a random selection and re-abstracting of cancer cases from the medical record. To decrease the possibility of misclassification, only microscopically confirmed primary cancers were included. By December 31, 1983, 1237 (6.9%) of the 17,944 women with first primary breast cancer developed a microscopically confirmed invasive or *in situ* second primary cancer; 55 third primary cancers and two fourth primaries also were identified. Basal and squamous cell carcinomas of the skin were excluded.

The observed number of cancers was compared to the expected number of cancers, calculated using person-years accumulated in each 5-year age-, race-, sex-, and year of diagnosis-group multiplied by the appropriate age-, sex-, race-, year of diagnosis-, site-specific incidence rates for Metropolitan Detroit. Person-years of risk were accumulated from the time of first breast cancer diagnosis to date of death or last contact for those women not developing a second primary or until date of diagnosis of the subsequent primary cancer. A total of 66,823 person-years of risk were accumulated; mean follow-up time was 4.0 years for white women and 3.4 years for black women. Standardized incidence ratios (SIRs) were calculated as the observed number of cancers divided by the expected number of cancers [9]. The 95% confidence intervals (CI) for the SIRs were calculated assuming that the observed number of cancers follows a Poisson distribution [10]. SIRs of one (confidence intervals that include 1.00) indicate no excess risk of subsequent cancer. This analysis was repeated for a number of different subgroups of women. In an effort to reduce possible misclassification, women with less than one month of follow-up, as well as those with less than one year of follow-up, were excluded. To evaluate long-term risk of subsequent primary cancer, the analysis was repeated using women with at least five years of follow-up. For all women, regardless of length of follow-up, the analysis was repeated by age at first diagnosis of the breast cancer (< 40, 40–49, 50–59, 60–69, and 70+ years) and by race. Results are presented for subsequent primary cancer sites with at least five cases diagnosed in the total cohort.

Results

The distribution of age at diagnosis and race for the study cohort is presented in Table 1. The incidence of all invasive second primary cancers was 1.8 times higher than the expected number (95% Confidence

Table 1. Age at diagnosis by race and multiple primary status

Age at diagnosis of first primary breast cancer	White		Black	
	One primary only (N = 14106) %	More than one primary (N = 1053)* %	One primary only (N = 2601) %	More than one primary (N = 184)* %
< 40	8.7	5.0	13.7	16.3
40–49	16.3	15.6	19.2	17.4
50–59	26.6	26.2	26.7	20.7
60–69	23.6	27.3	21.2	24.5
70+	24.8	25.9	19.2	21.2

* There were a total of 1237 women diagnosed with 1303 subsequent primary cancers (both *in situ* and invasive).

Interval = 1.68, 1.89) for the total sample of women (Table 2). Subsequent primary breast cancers occurred 3.8 times more often than expected (95% CI = 3.50, 4.11), while subsequent colon cancers were observed 24% more often than expected (95% CI = 1.00, 1.44) and cervical cancers 54% more often (95% CI = 1.01, 2.48). Elevated SIRs were seen for subsequent cancers of the uterine corpus (SIR = 1.28, 95% CI = 0.96, 1.63) and ovary (SIR = 1.45, 95% CI = 0.99, 1.99); however, these results were not significant at the 0.05 level. Subsequent *in situ* cancers of all sites were

Table 2. Observed (O) and expected (E) numbers of subsequent invasive cancers after diagnosis of an initial breast cancer

Site of subsequent invasive primary	O	E	SIR (O/E)	95% confidence interval
Buccal cavity and pharynx	14	9.71	1.44	(0.79, 2.42)
Stomach	20	15.49	1.29	(0.79, 1.99)
Colon	96	77.51	1.24	(1.00, 1.44)
Rectosigmoid junction	14	10.06	1.39	(0.76, 2.33)
Rectum	21	18.15	1.16	(0.72, 1.77)
Pancreas	16	20.69	0.77	(0.44, 1.25)
Lung and bronchus	72	69.25	1.04	(0.82, 1.31)
Soft tissues	5	2.38	2.10	(0.68, 4.91)
Melanoma of the skin	9	7.92	1.14	(0.52, 2.16)
Breast	624	164.28	3.80	(3.50, 4.11)
Uterine cervix	27	17.51	1.54	(1.01, 2.48)
Uterine corpus	67	52.52	1.28	(0.96, 1.63)
Ovary	39	26.82	1.45	(0.99, 1.99)
Vulva	5	3.74	1.34	(0.43, 3.13)
Urinary bladder	17	17.32	0.98	(0.57, 1.57)
Kidney	12	10.56	1.14	(0.59, 1.99)
Brain	5	6.61	0.76	(0.25, 1.78)
Thyroid	10	6.66	1.50	(0.72, 2.76)
Non-Hodgkin's lymphoma	16	19.43	0.82	(0.47, 1.33)
Multiple myeloma	6	8.61	0.70	(0.26, 1.53)
Leukemia	19	15.45	1.23	(0.74, 1.92)
Ill-defined sites	5	24.02	0.21	(0.07, 0.49)
All sites*	1106	621.61	1.78	(1.68, 1.89)

* Women with more than one subsequent primary cancer are included only once in the all sites total.
N = 17,944 women followed after diagnosis of first primary breast cancer.

Table 3. Observed (O) and expected (E) numbers of subsequent invasive cancers after diagnosis of an initial breast cancer by race

Site of subsequent invasive primary	White women			
	O	E	SIR (O/E)	95% confidence interval
Buccal cavity and pharynx	12	8.38	1.43	(0.74, 2.50)
Stomach	17	13.08	1.30	(0.76, 2.08)
Colon	81	67.00	1.21	(0.96, 1.50)
Rectosigmoid junction	12	9.02	1.33	(0.69, 2.32)
Rectum	19	16.20	1.17	(0.70, 1.83)
Pancreas	13	17.26	0.75	(0.40, 1.28)
Lung and bronchus	61	59.99	1.02	(0.78, 1.31)
Soft tissues	4	2.01	1.99	(0.54, 5.09)
Melanoma of the skin	7	7.72	0.91	(0.37, 1.88)
Breast	530	146.53	3.62	(3.32, 3.94)
Uterine cervix	18	12.81	1.41	(0.83, 2.23)
Uterine corpus	63	48.98	1.28	(0.98, 1.64)
Ovary	35	24.18	1.45	(1.01, 2.02)
Vulva	4	3.37	1.19	(0.32, 3.04)
Urinary bladder	16	15.70	1.02	(0.58, 1.66)
Kidney	11	9.42	1.17	(0.59, 2.09)
Brain	5	6.21	0.81	(0.26, 1.89)
Thyroid	9	6.00	1.50	(0.69, 2.85)
Non-Hodgkin's lymphoma	15	17.85	0.84	(0.47, 1.39)
Multiple myeloma	4	6.56	0.61	(0.17, 1.56)
Leukemia	17	13.67	1.24	(0.72, 1.98)
Ill-defined sites	4	21.13	0.19	(0.05, 0.49)
All sites*	946	546.41	1.73	(1.62, 1.84)

* Women with more than one subsequent primary cancer are included only once in the all sites total.
N = 15,159 women followed after diagnosis of first primary breast cancer.

Site of subsequent invasive primary	Black women			
	O	E	SIR (O/E)	95% confidence interval
Buccal cavity and pharynx	2	0.24	8.33	(1.01, 30.07)
Stomach	3	2.41	1.25	(0.26, 3.65)
Colon	15	10.51	1.43	(0.80, 2.36)
Rectosigmoid junction	2	1.04	1.93	(0.23, 6.97)
Rectum	2	1.95	1.03	(0.12, 3.68)
Pancreas	3	3.42	0.88	(0.18, 2.57)
Lung and bronchus	11	9.26	1.19	(0.60, 2.13)
Soft tissues	1	0.38	2.67	(0.07, 14.83)
Melanoma of the skin	2	0.20	10.08	(1.22, 36.39)
Breast	94	17.75	5.30	(4.29, 6.49)
Uterine cervix	9	4.71	1.91	(0.88, 3.62)
Uterine corpus	4	3.54	1.13	(0.31, 2.89)
Ovary	4	2.64	1.51	(0.41, 3.86)
Vulva	1	0.37	2.70	(0.07, 15.00)
Urinary bladder	1	1.63	0.62	(0.02, 3.44)
Kidney	1	1.13	0.88	(0.02, 4.89)
Thyroid	1	0.66	1.51	(0.04, 8.39)
Non-Hodgkin's lymphoma	1	1.58	0.63	(0.02, 3.50)
Multiple myeloma	2	2.06	0.97	(0.12, 3.50)
Leukemia	2	1.78	1.12	(0.14, 4.04)
Ill-defined sites	1	2.90	0.35	(0.01, 1.94)
All sites*	160	75.21	2.13	(1.81, 2.49)

* Women with more than one subsequent primary cancer are included only once in the all sites total.
N = 2,785 women followed after diagnosis of first primary breast cancer.

detected 3.98 times more often than expected (95% CI = 3.35, 4.70). One hundred and fourteen of these 140 *in situ* cancers were found in the breast (SIR = 16.04, 95% CI = 12.94, 19.28).

Excess risk of subsequent invasive breast cancer was seen among black (SIR = 5.3, 95% CI = 4.29, 6.49) and white women (SIR = 3.6, 95% CI = 3.32, 3.94) (Table 3). Cancers of the ovary occurred significantly more often than expected only among white women (SIR = 1.45, 95% CI = 1.01, 2.02). While SIRs were elevated for this site among black women, the results were not statistically significant. Among black women, SIRs for melanomas (10.08) and cancers of the buccal cavity and pharynx (8.33) were greater than one ($p < 0.05$); however, there were only two observed cases for each of these sites. Risk for subsequent *in situ* cancers of all sites did not differ by race; the SIR for white women was 4.01 (95% CI = 3.31, 4.94) and the SIR for black women was 3.89 (95% CI = 2.54, 5.70).

Risk of subsequent primary cancer after first primary breast cancer varied by age at diagnosis of the first breast cancer and by length of follow-up. For subsequent breast cancers among black and white women, a decreasing trend in the SIR was seen with increasing age at diagnosis of the first primary breast cancer (Table 4). The SIR for black women was more than double that for white women in the youngest age group. A similar age pattern was seen among white women with subsequent ovarian cancer, with highest risk among white women first diagnosed with breast cancer before 40 years of age (SIR = 7.14, 95% CI = 1.47, 20.88).

Table 4. Observed (O) and expected (E) numbers of subsequent invasive breast cancers after diagnosis of an initial breast cancer by age at first diagnosis and race

Age at diagnosis of first primary breast cancer	N*	Total			
		O	E	SIR (O/E)	95% confidence interval
<40	1670	55	3.99	13.80	(10.37, 17.98)
40–49	2990	119	24.06	4.95	(4.10, 5.92)
50–59	4766	160	45.18	3.54	(3.01, 4.13)
60–69	4207	141	45.41	3.11	(2.62, 3.67)
70+	4311	149	45.64	3.27	(2.76, 3.84)
Age at diagnosis of first primary breast cancer	N*	White women			
		O	E	SIR (O/E)	95% confidence interval
<40	1283	35	3.22	10.87	(7.55, 15.12)
40–49	2459	97	20.82	4.66	(3.78, 5.36)
50–59	4034	142	40.11	3.54	(2.98, 4.17)
60–69	3611	126	41.10	3.07	(2.56, 3.66)
70+	3772	130	41.28	3.15	(2.63, 3.74)
Age at diagnosis of first primary breast cancer	N*	Black women			
		O	E	SIR (O/E)	95% confidence interval
<40	387	20	0.77	26.15	(15.94, 40.41)
40–49	531	22	3.25	6.78	(4.24, 10.27)
50–59	732	18	5.07	3.55	(2.10, 5.61)
60–69	596	15	4.31	3.48	(1.94, 5.74)
70+	539	19	4.35	4.36	(2.63, 6.81)

* N = number of women followed after diagnosis of first primary breast cancer.

Ovarian cancer risk remained fairly constant for white women first diagnosed between 40 and 69 years of age (SIRs ranged from 1.5 to 1.7), then dropped to 0.74 for women diagnosed at 70 years of age or older; however, none of these SIRs were significantly different from one. There were no significant trends in risk with changing age at first diagnosis for subsequent cervical, uterine corpus, or colon cancer.

Approximately 39% of the subsequent primary cancers were diagnosed within one year of first primary breast cancer diagnosis; but a large proportion, approximately 24% of all second primaries, were actually diagnosed within a month of first diagnosis. When women with less than one month of follow-up are excluded from the analysis, the incidence of subsequent invasive breast cancer remained elevated, although the SIR decreased to 2.57 (95% CI = 2.33, 2.83) (Table 5). The same trend was seen for all invasive cancers combined (SIR = 1.35, 95% CI = 1.26, 1.44) and all *in situ* cancers combined (SIR = 2.25, 95% CI = 1.81, 2.81). Excluding women with less than one year of follow-up further reduces the excess risk of breast cancer (SIR = 2.13, 95% CI = 1.91, 2.37), invasive cancers of all sites combined (SIR = 1.12, 95% CI = 1.04, 1.21), and *in situ* cancers of all sites combined (SIR = 1.61, 95% CI = 1.21, 2.10). No excess risk for subsequent invasive cancers of sites other than breast was apparent in either of these two subgroups of women. Eighteen percent of the white women and 14% of the black women were followed for more than five years before the occurrence of their second primary cancer (Table 5). After five years of follow-up no excess risk of invasive or *in situ* second primary cancers was observ-

Table 5. Observed (O) and expected (E) numbers of subsequent invasive cancers after diagnosis of an initial breast cancer by length of follow-up

Site of subsequent invasive primary	Followed at least one month			
	O	E	SIR (O/E)	95% confidence interval
Buccal cavity and pharynx	10	8.79	1.14	(0.55, 2.10)
Stomach	19	15.21	1.25	(0.75, 1.95)
Colon	85	76.16	1.12	(0.90, 1.39)
Rectosigmoid junction	13	9.88	1.32	(0.70, 2.26)
Rectum	20	17.83	1.12	(0.68, 1.73)
Pancreas	15	20.32	0.74	(0.41, 1.22)
Lung and bronchus	63	68.06	0.93	(0.71, 1.19)
Soft tissues	4	2.34	1.71	(0.47, 4.37)
Melanoma of the skin	7	7.79	0.90	(0.36, 1.86)
Breast	420	163.20	2.57	(2.33, 2.83)
Uterine cervix	17	17.25	0.99	(0.58, 1.58)
Uterine corpus	52	51.66	1.01	(0.75, 1.33)
Ovary	33	26.37	1.25	(0.86, 1.76)
Vulva	5	3.68	1.36	(0.44, 3.18)
Urinary bladder	16	17.03	0.94	(0.54, 1.53)
Kidney	10	10.38	0.97	(0.47, 1.78)
Brain	4	6.49	0.62	(0.17, 1.59)
Thyroid	8	6.56	1.22	(0.53, 2.40)
Non-Hodgkin's lymphoma	13	19.08	0.68	(0.36, 1.16)
Multiple myeloma	5	8.46	0.59	(0.19, 1.38)
Leukemia	16	15.17	1.05	(0.60, 1.70)
Ill-defined sites	5	23.60	0.21	(0.07, 0.49)
All sites*	838	619.34	1.35	(1.26, 1.44)

* Women with more than one subsequent primary cancer are included only once in the all sites total.

N = 17,233 women followed after diagnosis of first primary breast cancer.

ed. In fact, SIRs of less than one were seen for all of the specific sites analyzed, as well as for all invasive sites combined (SIR = 0.54, 95% CI = 0.47, 0.62) five years after initial diagnosis.

Discussion

The results from this study support findings from other studies showing that women with first primary breast cancer are at increased risk of subsequent primary cancers, particularly of the breast, colon, ovary, and cervix [1–7]. The occurrence of two distinct cancers within an individual might suggest that a common risk factor is acting to increase risk for both cancer sites. Those environmental factors associated with the first primary breast cancer in the women studied, such as reproductive history or dietary practices, are likely to be associated with risk of cancer in the remaining breast, and may be associated with risk of cervical, colon, and ovarian cancers.

Black women in this population-based study experienced higher risk of subsequent breast cancer than white women (SIR of 5.3 versus 3.6). This finding is consistent with the work of Newell *et al.* [3] who reported a relative risk for second primary breast cancer of 1.8 for white females and 3.3 for black females in a hospital-based study. Newell *et al.* [3] did not examine risk by age at diagnosis. In the present study, black/white differences in subsequent risk of breast cancer were greatest for women diagnosed before age 40. It is interesting to note that in the Metropolitan Detroit area, although the 1986 age-adjusted incidence rates for breast cancer are higher among white women than among black women, age-specific rates are higher among black women before age 45. Black women

Table 5. (Continued).

Site of subsequent invasive primary	Followed at least one year			
	O	E	SIR (O/E)	95% confidence interval
Buccal cavity and pharynx	8	8.50	0.94	(0.41, 1.85)
Stomach	15	14.70	1.02	(0.57, 1.68)
Colon	73	73.78	0.99	(0.78, 1.25)
Rectosigmoid junction	11	9.58	1.15	(0.58, 2.06)
Rectum	17	17.26	0.99	(0.58, 1.58)
Pancreas	14	19.65	0.71	(0.39, 1.19)
Lung and bronchus	56	65.81	0.85	(0.64, 1.10)
Soft tissues	4	2.27	1.76	(0.48, 4.50)
Melanoma of the skin	5	7.55	0.66	(0.21, 1.54)
Breast	337	158.46	2.13	(1.91, 2.37)
Uterine cervix	14	16.72	0.84	(0.46, 1.41)
Uterine corpus	41	50.12	0.82	(0.59, 1.11)
Ovary	25	25.53	0.98	(0.63, 1.45)
Vulva	5	3.56	1.41	(0.46, 3.29)
Urinary bladder	13	16.49	0.79	(0.42, 1.35)
Kidney	5	10.04	0.50	(0.16, 1.17)
Brain	2	6.29	0.32	(0.04, 1.16)
Thyroid	6	6.35	0.95	(0.35, 2.07)
Non-Hodgkin's lymphoma	13	18.47	0.70	(0.37, 1.20)
Multiple myeloma	3	8.19	0.37	(0.08, 1.08)
Leukemia	16	14.70	1.09	(0.62, 1.77)
Ill-defined sites	3	22.88	0.13	(0.03, 0.38)
All sites*	676	603.26	1.12	(1.04, 1.21)

* Women with more than one subsequent primary cancer are included only once in the all sites total.
N = 14,278 women followed after diagnosis of first primary breast cancer.

also have higher incidence rates of breast cancer than white women over the age of 74. This suggests that exposure to particular risk factors and/or the significance of those factors for breast cancer may vary by age and race. Gray *et al.* [11] hypothesize that the elevated risk of invasive breast cancer among young black women may be due in part to black women as a group having an earlier age at menarche than white women. If this is the case, then age at menarche may play a role in the risk of multiple breast cancers as well.

Multiple cancer occurrence also might imply that certain persons have an inherited predisposition or susceptibility to cancer. Families at highest risk of having a genetic form of breast cancer have been observed to have breast cancer in younger family members [12]. Another characteristic of familial breast cancer is an increased risk of multiple primary cancers, especially in the breast [13]. Both young black and white women diagnosed with breast cancer at an early age were shown to be at high risk of developing a subsequent primary breast cancer soon after their initial breast cancer diagnosis, suggesting a familial component to risk. Higher risk of subsequent breast cancer among young black women than young white women suggests that genetic susceptibility to breast cancer may vary by race. Few studies have been completed to fully evaluate the prevalence of family history of breast cancer among blacks. Further research is needed to describe family patterns of cancer risk by race in geographic regions with large black populations. These findings suggest that young women with a personal history of breast cancer would benefit from continued medical surveillance and screening for breast cancer, beginning at their first diagnosis, so that subsequent primary cancers are detected in early stages.

Table 5. (Continued).

Site of subsequent invasive primary	Followed at least five years			
	O	E	SIR (O/E)	95% confidence interval
Buccal cavity and pharynx	5	5.17	0.97	(0.31, 2.27)
Stomach	1	8.93	0.11	(0.003, 0.61)
Colon	34	45.08	0.75	(0.52, 1.05)
Rectosigmoid junction	4	5.91	0.68	(0.19, 1.74)
Rectum	5	10.62	0.47	(0.15, 1.10)
Pancreas	4	11.91	0.34	(0.09, 0.87)
Lung and bronchus	16	40.08	0.40	(0.23, 0.65)
Soft tissues	0	–	–	–
Melanoma of the skin	1	4.58	0.22	(0.01, 1.22)
Breast	90	98.22	0.92	(0.74, 1.13)
Uterine cervix	3	10.41	0.29	(0.06, 0.85)
Uterine corpus	12	31.72	0.38	(0.20, 0.66)
Ovary	7	15.84	0.44	(0.18, 0.91)
Vulva	1	2.18	0.46	(0.01, 2.56)
Urinary bladder	4	10.17	0.39	(0.11, 1.00)
Kidney	1	6.12	0.16	(0.004, 0.89)
Brain	1	3.88	0.26	(0.01, 1.44)
Thyroid	3	3.97	0.76	(0.16, 2.22)
Non-Hodgkin's lymphoma	3	11.28	0.27	(0.06, 0.79)
Multiple myeloma	1	4.99	0.20	(0.01, 1.11)
Leukemia	7	9.01	0.78	(0.31, 1.61)
Ill-defined sites	0	–	–	–
All sites*	202	376.25	0.54	(0.47, 0.62)

* Women with more than one subsequent primary cancer are included only once in the all sites total.
N = 5,411 women followed after diagnosis of first primary breast cancer.

Familial factors also may be important in the occurrence of second primary ovarian cancers after breast cancer as this association is stronger among the women first diagnosed with breast cancer before age 40. Familial associations between breast and ovarian cancers have been demonstrated [14]. Prior *et al.* [15] also report excess risk of subsequent ovarian cancers among breast cancer cases diagnosed before age 45, but not after that age. Hormonal factors acting before menopause might affect risk of both breast and ovarian cancers.

For most other sites, there were too few cases to fully evaluate racial differences in risk, although SIRs for black and white women generally were in the same direction. Exceptions were seen for subsequent melanomas of the skin and cancers of the buccal cavity and pharynx where excess risk was observed among black women and not among white women. Excess risk for these sites was reported in Connecticut [6, 16] for the total population of breast cancer patients, not stratified by race. Melanomas of the skin are rare among blacks; the age-adjusted incidence rates (standardized to the 1970 U.S. standard million) for 1986 in Metropolitan Detroit are 0.4 per 100,000 for black women and 8.7 per 100,000 for white women. Risk of superficial spreading melanomas have been associated with use of oral contraceptives and first live birth after age 30 [17]. Late age at first birth also is a well-recognized risk factor for breast cancer [18], suggesting common hormonal mechanisms in the development of melanomas and breast cancer. An association between alcohol consumption and risk of melanomas [19] and cancers of the buccal cavity and pharynx [20] also have been reported [21]. The association between alcohol consumption and breast cancer risk is equivocal [22–24]. Although only two subsequent melanomas and two subsequent cancers of the buccal cavity and pharynx were observed among black woman, this was more than 8 times higher than the expected numbers. These findings raise the possibility of racial differences in exposure to risk factors common to breast cancer and malignant melanomas of the skin and cancers of the buccal cavity and pharynx.

When possible misclassification was addressed by excluding women with less than one month and less than one year of follow-up, excess risk of subsequent primary breast cancer was still evident. Although risk beyond five years was difficult to analyze because of the small numbers of women followed for this length of time, no excess risk was apparent at five or more years after first breast cancer diagnosis. In a larger population-based study of multiple primary cancers in Connecticut [6], excess risk for subsequent cancers of all sites excluding the breast was not apparent until 5–9 years after initial breast cancer diagnosis. It is possible that excess risk for some sites will occur with increased follow-up of this study population. The excess of cancers diagnosed soon after the initial breast cancer may be due to increased medical surveillance of this cohort. Cancers which, under normal circumstances, may not be diagnosed for a number of years, may be detected early. The excess risk of *in situ* cancers lends support to this theory. Misclassification of metastatic or recurrent disease as independent primaries, particularly in the case of subsequent breast cancers, also may be a problem. Length of time between first and second primary has been used in other studies as a criterion for determining whether a subsequent cancer is a new primary. Even with the exclusion of women followed for less than one month or one year, the excess risk of subsequent breast cancer is still seen. Restricting analyses to microscopically confirmed cancers and having uniform guidelines on the classification of multiple primaries can reduce misclassification bias. It is unlikely that misclassification could explain the large excess risk observed for subsequent breast cancers in the population described.

There are limitations in the statistical analysis that must be considered in evaluating these results. Multiple statistical tests were carried out, increasing the likelihood that some findings were significant by chance. This does not seem to have been a substantial problem in this study, as the results are consistent with other work in this area.

Population-based cancer registries provide an excellent opportunity to study the occurrence of multiple primary cancers over long periods of time. This study adds new, population-based evidence of exceptionally high risk of multiple primary breast cancers among black women under the age of 40.

Future investigations of multiple primary cancers among breast cancer patients should include information about risk factors other than those available from medical records to more fully understand common etiologic factors and inherited susceptibility thought to increase risk of second cancer occurrence among black and white women. Since 62.7% of women diagnosed with their first breast cancer survive for at least 10 years [25], an important extension of this study will be to determine the risk of multiple primary cancers at 10 years after diagnosis.

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