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Clustering of Individuals with both Breast and Ovarian Cancer

A Possible Indicator of BRCA Founder Mutations

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Acta Oncologica Vol. 41, No. 2, pp. 153–157, 2002

In a cohort of 60 436 women with a diagnosis of invasive breast carcinoma and known to reside in Sweden in 1960, 321 had a subsequent diagnosis of ovarian carcinoma. Assuming no correlation between the two cancers, one would expect that 191 women would develop ovarian cancer (standardized incidence ratio (SIR) 1.7; 95% confidence interval 1.5–1.9). Women with breast cancer before 40 years of age were at highest risk for developing ovarian cancer (SIR 4.5). Between 40 and 49 years of age, the SIR was 1.9, and at 50 years of age or older, the SIR was 1.3. Most of the excess in ovarian cancer occurred in southern Sweden. The geographic distribution of these cases coincided with the distribution of families with known BRCA1 and BRCA2 gene mutations. These results suggest that genetic factors account for the excess in ovarian cancer that occurs in breast cancer patients and that geographic clustering of patients who have both breast and ovarian cancer may indicate the presence of a BRCA founder mutation.

Received 9 October 2001
Accepted 17 January 2002

The hereditary breast and ovarian cancer syndrome is characterized by the early onset of cancer, involvement of multiple family members with these cancers, and the occurrence of bilateral breast carcinoma or breast and ovarian carcinoma in the same individual (1). Major identified causes of this syndrome are constitutional mutations in the BRCA1 and BRCA2 genes (2, 3). In closed populations, as in Iceland or among Ashkenazi Jews, mutations of these genes occur frequently (24–28%) among unselected women with early onset of breast cancer (4–6). The frequency seems to be much lower in outbred populations (7–11).

In Sweden, many different mutations of the BRCA1 and BRCA2 genes have been detected; most of these are restricted to a few families. Almost all of the families with the most common mutation in Sweden, BRCA1 3171ins5, originate from a limited geographic area along the west coast of Sweden (12). Other common BRCA1 mutations in Sweden, 2594delC and 1201-1211del, have been detected primarily in families from southern Sweden (13), Denmark and Norway (14). Another BRCA1 mutation, 1806C > T, occurs primarily in southern Sweden as well as other European countries (14). Yet another BRCA1 mutation, 3745 delT, apparently originates in northern Sweden and Finland (15). In general, families in Sweden with known BRCA1/2 mutations live in southern and southwestern Sweden; relatively few live in northern Sweden.

A possible marker of the hereditary breast and ovarian cancer syndrome is the occurrence of ovarian carcinoma in a patient with breast cancer. In our previous study of families with BRCA1 gene mutation (3171 ins5), 8 out of 39 women with breast cancer (20%) also developed ovarian cancer and 8 had bilateral breast cancer (12). Since bilateral breast cancer is frequently non-familial (16), we evaluated the geographic distribution of the risk of developing ovarian cancer in a population of women with breast cancer and analyzed whether the increased risk coincided with the geographic distribution of known BRCA1 founder mutations.

MATERIAL AND METHODS

A total of 60 436 women with a diagnosis of invasive adenocarcinoma of the breast were identified in the Swedish Cancer Registry from 1960 to 1997; the women were born between 1920 and 1960 and information regarding their residence was available in the 1960 census.

 ISSN 0284-186X

Additional information was obtained from the Emigration Registry, the Cause-of-Death Registry and the National Population Registry of 1997. To ensure patient anonymity, personal identification numbers were replaced with random numbers by the Central Bureau of Statistics. There was a total of 482138 person years of follow-up. The mean patient age at the time of breast cancer diagnosis was 53.7 years (median 53.1, range 12–77 years). Women who developed a subsequent ovarian carcinoma were identified within this cohort.

The cases were divided into four groups according to age at the time of breast cancer diagnosis; 0–39 years, 40–49 years, 50–59 years, and ≥ 60 years of age. For geographic comparisons, we divided the place of residence in 1960 into areas corresponding to the present six healthcare regions. The three largest cities, Stockholm, Gothenburg and Malmö, were reported separately and excluded from their respective healthcare regions since their populations are probably heavily influenced by migration from other areas.

Statistical methods

Follow-up of the breast cancer patients started from the date of the first breast cancer diagnosis according to the Cancer Registry report and continued until a diagnosis of adenocarcinoma of the ovary, the first date of emigration, the date of death or to 31 December 1997, whichever occurred first. Expected numbers were based on the numbers of person-years at risk and the national incidence rates for each 5-year age group and every 5 years of follow-up since1960. The national incidence rates were derived from the total Swedish female population with a known place of residence in the census of 1960 to avoid any bias from the selection process of the study population. Standardized incidence ratios (SIR) were calculated as the ratio between the observed and the expected number of ovarian cancers. Confidence intervals were calculated assuming the observed numbers to be Poisson distributed. Poisson regression with maximum likelihood methods were performed using the Amfit software of the Epicure Statistical package (17). No adjustment for multiple comparisons was made for the calculation of probabilities or confidence intervals.

RESULTS

Among the 60436 women with breast cancer reported to the Swedish Cancer Registry, 321 subsequently developed ovarian cancer. Assuming no correlation between breast and ovarian cancer, the expected number was 191, SIR 1.7 (95% confidence interval (CI) 1.5–1.9). Patient age at the time of the initial breast cancer diagnosis was a significant predictive factor for the development of ovarian cancer ($p < 0.0001$, Table 1). SIR was significantly increased in all age groups. The highest risk, however, was found in patients younger than 40 years of age (SIR 4.5; 95% CI 3.3–5.8). In patients aged 40–49 years, SIR was 1.9 (95% CI 1.6–2.2), whereas for the age groups 50–59 and 60+ years, SIR was 1.3 (95% CI 1.0–1.6 and 1.0–1.7, respectively).

Details of the number of breast cancer patients, person-years, number of ovarian cancers and SIR for each of the healthcare regions, with separate records for the three largest cities, are presented in Table 2. There was a significant variation in the SIRvalues of various regions ($p = 0.0007$). Although the SIR values of all regions were above unity, they were particularly increased in four regions and in one city, including the Uppsala–Örebro region, SIR 1.6 (95% CI 1.2–2.0); the southeastern region, SIR 1.8 (95% CI 1.3–2.4); the western region, SIR 2.7 (95% CI 2.0–3.4) and the southern region, SIR 2.2 (95% CI 1.6–2.8) and Gothenburg, SIR 2.0 (95% CI 1.3–2.9).

In Table 3, SIR values are presented by age at the time of breast cancer diagnosis and geographic location. The SIR values varied significantly between different geographic regions for women under the age of 50 years ($p = 0.01$) but not to the same extent for women of 50 years of age or older ($p = 0.14$). Higher SIR values than the mean of the whole country were seen in women under the age of 50 within the three southern regions and the city of Gothenburg. The SIR values of the various geographic regions are given in the Fig. 1.

DISCUSSION

This study demonstrates that in a population of Swedish women with breast cancer diagnosed before the age of 50 years, a subsequent diagnosis of ovarian cancer is more

Table 1

Ovarian cancer following breast cancer by age at breast cancer diagnosis

Age, years	Breast cancer patients	Person-years at risk	Observed number of ovarian cancers	SIR (95% CI)
0–39	4 861	55 091	50	4.5 (3.3–5.8)
40–49	17 640	184 611	121	1.9 (1.6–2.2)
50–59	18 996	147 789	86	1.3 (1.0–1.6)
60	18 939	94 648	64	1.3 (1.0–1.7)
All	60 436	482 138	321	1.7 (1.5–1.9)

Table 2

*Standardised incidence ratio (SIR) for ovarian cancer following breast cancer according to health care regions (*three largest cities excluded from the regions and reported separately)*

Region	Breast cancer patients	Person-years at risk	Observed number of ovarian cancer	SIR (95% CI)
North	6 801	51 676	25	1.3 (0.8–1.8)
Uppsala–Örebro	12 998	101 211	63	1.6 (1.2–2.0)
Stockholm–Gotland	4 687	38 778	16	1.0 (0.6–1.6)
-Stockholm*	7 578	64 966	33	1.3 (0.9–1.7)
Southeast	6 943	54 757	38	1.8 (1.3–2.4)
West	7 000	54 347	57	2.7 (2.0–3.4)
-Gothenburg*	3 718	30 781	25	2.0 (1.3–2.9)
South	8 369	64 943	55	2.2 (1.6–2.8)
-Malmö*	2 342	20 679	9	1.1 (0.5–2.0)
All	60 436	482 138	321	1.7 (1.5–1.9)

common than would be expected. In a previous but smaller study, Adami et al. also found a significantly increased risk for developing ovarian cancer (relative risk 2.2; 95% CI 1.5–3.3; n = 22) in women with breast cancer diagnosed before 50 years of age (18). They attributed their finding to metastatic breast cancer in the abdomen that was misdiagnosed as primary ovarian cancer. However, metastatic breast cancer in the abdomen is unlikely to occur solely in the younger age group. Pathologists could conceivably overdiagnose breast carcinoma metastases within the abdomen and underdiagnose subsequent ovarian carcinomas in women with established hereditary breast and ovarian cancer. However, histologic reevaluation of multiple primary tumors reported to the Swedish Cancer Registry revealed that 98% of the second malignancies were correctly classified (19).

There are confounding factors that could lead to erroneous conclusions in a registry study such as ours. The cases may vary systematically, depending on different local and logistic reasons. For example, establishment of a diagnosis of ovarian carcinoma depends on actions taken by the clinicians when a woman with a previously known breast cancer also develops an intra-abdominal mass. A clinical or pathologic misdiagnosis of advanced ovarian carcinoma as metastatic breast cancer could occur, and vice versa. The net effect of such errors is difficult to estimate. In addition, breast cancer patients during this period might have been treated with ovarian ablation as an adjunct to surgery or as treatment of advanced disease. If, however, there was no correlation between heredity and oophorectomy, the comparisons would not be biased. Oophorectomy may have been used to a varying extent in different geographic areas, thereby contributing to geographic differences in the risk of developing subsequent ovarian cancer. However, the aforementioned factors do not fully account for the geographic differences observed in this study.

Table 3

*Ovarian cancer following breast cancer in healthcare regions. Standardized incidence ratio (SIR) (95% confidence interval) is given for patients under 50, or ≥50 years of age at breast cancer diagnosis and for all ages (*three biggest cities excluded from the regions and reported separately)*

Region	Age <50 years	Aged ≥50 years	All ages
North	1.4 (0.8–2.4)	1.1 (0.6–1.9)	1.3 (0.8–1.8)
Uppsala–Örebro	1.8 (1.2–2.5)	1.5 (1.0–2.0)	1.6 (1.2–2.0)
Stockholm–Gotland	1.5 (0.7–2.7)	0.7 (0.3–1.4)	1.0 (0.6–1.6)
-Stockholm	1.8 (1.1–2.8)	0.9 (0.5–1.4)	1.3 (0.9–1.7)
Southeast	2.3 (1.4–3.5)	1.4 (0.8–2.1)	1.8 (1.2–2.4)
West	4.1 (2.8–5.6)	1.8 (1.1–2.6)	2.7 (2.0–3.5)
-Gothenburg	2.8 (1.6–4.6)	1.5 (0.8–2.5)	2.0 (1.3–2.9)
South	2.9 (2.0–4.1)	1.7 (1.1–2.4)	2.2 (1.6–2.8)
-Malmö	1.8 (0.7–3.6)	0.6 (0.1–1.6)	1.1 (0.5–2.0)
All	2.3 (1.9–2.6)	1.3 (1.1–1.5)	1.7 (1.5–1.9)

The excess of ovarian carcinoma occurring among women with previously diagnosed breast cancer reflects common causes of these diseases. One common link between the risk of these two cancer sites is the fertility pattern. The risk of ovarian cancer as well as of breast cancer is increased in women with no or few pregnancies. In the latter disease, an early age at the first pregnancy seems to be more important than the number of pregnancies. The protective effect of an early pregnancy is, however, largest in postmenopausal women, as we have shown in another study based on the same population (20). In the present study, the highest excess of ovarian cancers was found in women who were under 40 year of age at the time of the breast cancer diagnosis. This is compatible with a common genetic cause for the two tumor types. This impression is supported by our observation that the geographic concentration of excess ovarian cancer in women under 50 years of age in the three southernmost healthcare regions coincides with the geographic distribution of families with BRCA1 and BRCA2 gene mutations (12, 13).

Women within southwestern Sweden had the highest risk of developing subsequent ovarian cancer. This finding may well reflect the occurrence of the most common

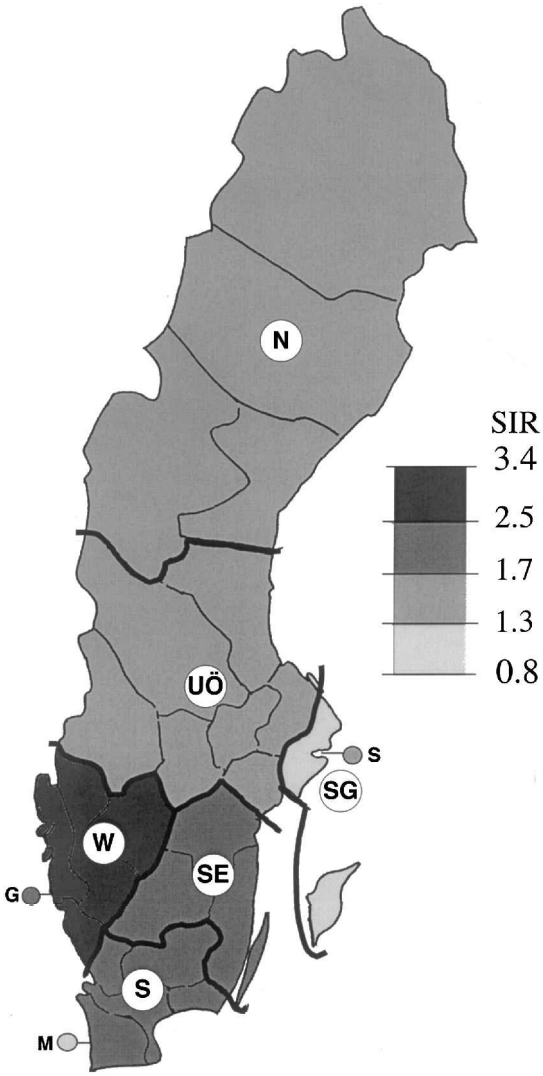

Fig. 1. Standardized incidence ratio (SIR) of ovarian cancer following diagnosis of breast cancer in the healthcare regions of Sweden and in the largest cities. The steps in the grey scale represent 0.5, 0.75, 1.0, 1.5 and 2 times the SIR for the whole of Sweden (SIR = 1.7). The healthcare regions: N = North of Sweden; UÖ = Uppsala–Örebro; SG = Stockholm–Gotland; SE = Southeast of Sweden; W = West of Sweden; and S = South of Sweden. The largest cities are S (Stockholm), G (Göteborg) and M (Malmö).

Swedish BRCA1 (3171ins5) mutation that seems to have originated from this region. Further light on the issue of the geographical distribution might be derived from studies within the Family Cancer Database, which contains information on cancer cases in individuals born after 1931 and in their parents and siblings, as has recently been described by Hemminki (21).

The relatively low number of cases in the registry study does not allow a statistically meaningful subgrouping into smaller geographic areas. We have, however, initiated a study to screen all individuals in the western region with both breast and ovarian cancer for the presence of the founder mutation BRCA1 3171ins5. Further study of archival material will help to reveal the true incidence of this founder mutation among breast and ovarian cancer cases.

In conclusion, there is a significantly increased risk of developing subsequent ovarian cancer among women with breast cancer, particularly if the breast cancer was diagnosed before 50 years of age. The finding that the highest risk of developing both breast and ovarian cancer coincides with geographic areas where the BRCA1 founder mutation appears to be most common suggests that clustering of these two cancer types can be used as an indicator of BRCA founder mutations.

ACKNOWLEDGEMENTS

Funding for this research was obtained from the Swedish State under the LUA agreement and the King Gustav V Jubilee Clinic Cancer Research Foundation.

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