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Risk of Second Non Breast Malignancies (SNBM) in Relation to *Brca1* And *Brca2* Mutation Status Following Breast-Conserving Surgery and Radiotherapy

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Abstract: Women from hereditary breast cancer families with *BRCA1/2* germline mutation are at increased risk for contralateral breast cancer (BC) and for ovarian cancer (OC). It is less clear whether mutation status influences the rate of SNBM other than OC. In addition, little is known on the risk of OC in individuals from hereditary BC families without identified *BRCA* mutation. Our purpose was to answer to these two questions. We retrospectively analysed a cohort of women with small cancers treated with breast conserving surgery and radiotherapy at our Institut from 1981 to 2000. The studied population was matched using strict criteria. *BRCA1/2* carriers had more SNBM than the French women population (FWP) (SIR=1099.2 [354.3-2565.4], $p<10^{-3}$); there were no differences between non carriers or controls and the FWP (SIR=149.3 [30.0-436.2] and SIR=80 [21.5-204.7], respectively). The *BRCA1/2* carriers and non carriers had more OC than the FWP (SIR=9640.1 [2593.6-24680.6]; $p<10^{-3}$ and SIR=1155.7 [129.8-4172.6]; $p<0.05$, respectively). We did not find any differences between the incidence rates of digestive, gynaecological and lung carcinoma between controls and the FWP, between *BRCA1/2* carriers and the FWP; and between non carriers and the FWP. After 9 year follow-up, our study showed that the rate of OC was increased in *BRCA1/2* mutation carriers as well as in non carriers compared to the FWP. We also showed that these patients were not at higher risk of SNBM other than OC. No differences have been found in the incidence rates of SNBM other than OC between controls and the FWP, between *BRCA1/2* carriers, non carriers and the general population, but more statistical power is needed to confirm these results.

Key words: *BRCA1/2* germline mutation, second non breast malignancies, ovarian cancer

INTRODUCTION

Women from hereditary breast cancer (BC) families who carry a *BRCA1* or *BRCA2* germline mutation are at increased risk for contralateral breast cancer and for ovarian cancer[1-3]. Special programs of follow-up, risk-reduction strategies, including intensive screening and/or risk-reducing surgery are developed and proposed to mutation carriers[3,4]. It is less clear whether mutation status influences the rate of second non breast malignancies (SNBM) other than ovarian cancer[5]. In addition, little is known on the risk of ovarian cancer in individuals from hereditary breast cancer families without identified *BRCA* mutation. The purpose of this study was to answer to these two questions.

PATIENTS AND METHODS

We retrospectively analysed a cohort of women with small breast cancers treated with breast conserving surgery and radiotherapy at the Institut Curie from 1981 to 2000. These patients were invited to attend the family cancer clinic of our institute between 1990 and 2001 if they presented with a familial history of breast or ovarian cancer. Selection criteria and the procedure used for molecular testing, as well as the way to obtain information such as family cancers, age at cancer diagnosis of relatives and age at death or current age have been reported previously[6,7]. Molecular testing offered to women who presented with one of the following family criteria: (i) two first-degree relatives affected with cancer, with at least either one with invasive breast cancer before 41 years or one with ovarian cancer at any age and (ii) at least three first- or second-degree relatives from the same lineage affected with invasive breast or ovarian cancer at any age. The index case was one of the affected family members. The probability of being carrier of a breast cancer predisposing allele mutation was estimated by taking into account the segregation parameters of Claus modified by Easton and by using the MLINK program[8,9]. After informing the patients about the aims and the limits of breast cancer genetic testing, a blood sample was collected with their written consent. One hundred thirty one patients (with 136 breast cancers) were tested. All of them underwent conservative surgery and radiotherapy in our hospital. They were

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matched to 261 control breast cancer patients (with 271 tumors) without family history (sporadic cases), taken from a prospectively registered population of 9179 patients in the Institut Curie's breast cancer database[2]. All of them had been treated conservatively from 1981 to 1999 at the Institut Curie. Matching was performed on an individual basis: for each case two controls were randomly selected. Matching factors included the age at diagnosis, year of treatment and period of follow-up: the follow-up of controls was at least equal to the time-interval between diagnosis and genetic testing in cases. *BRCA* status was unknown in all patients but one at the time of diagnosis and treatment. Clinical, pathological and outcome data were recorded. One control tumour has been excluded from the group because it did not respect selection criteria. All patients underwent breast-conserving treatment: wide surgical excision of the primary tumour and axillary lymph node dissection in most cases followed by breast irradiation and regional node irradiation when nodes were involved. More information concerning the genetic testing can be found in previously published data[2]. Incidence rates of each SNBM localisation found in our groups were estimated for 100,000 person-year (PY) in the whole population of patients and for each of the three groups (mutation carriers, non-carriers and controls). The incidence in each group was compared to the incidence in the French women population, using the standardized incidence ratio SIR[10].

RESULTS

BRCA1 and *BRCA2* mutations were found in 20.6% patients with a family history. Nineteen patients had a *BRCA1* mutation and 8 had a *BRCA2* mutation. Median follow-up for all 392 patients was 8.75 years (range 2.25 – 19.4 years). The follow-up of controls was at least equal to the time-interval between diagnosis and genetic testing in cases. The median patients' age at diagnosis was: 43 years (range, 26-60) in carriers, 43.5 (24-78) in non-carriers and 43 (23-79) in sporadic groups, respectively (p 0.92). There was no significant difference in menopausal status between the three groups (p 0.24). The 9-year SNBM-free interval rates were: 98% [97-100%] in the control group, 97% [94-100%] in the *BRCA1/2* non carriers and 79% [65-97%] in the BRCA1/2 carriers, respectively ($p<10^{-5}$). From 8 cancers in the "familial group", there were 5 in *BRCA1* and *BRCA2* mutation carriers (4 ovaries and 1 pancreatic carcinoma) and 3 in *BRCA1* and *BRCA2* non carriers (2 ovarian and 1 meningioma). In the group of controls, there were 3 gynaecological tumours (endometrium and cervix) and 1 small cell lung cancer. Overall, *BRCA1/2* carriers had more SNBM than the French women (SIR=1099.2 [354.3-2565.4], $p<10^{-3}$); we did not find any differences between *BRCA1/2* non carriers or controls and the French population (SIR=149.3 [30.0-436.2] and SIR=80 [21.5-204.7], respectively). The *BRCA1/2* carriers and *BRCA1/2* non carriers had more ovarian cancer than the French population (SIR=9640.1 [2593.6-24680.6]; $p<10^{-3}$ and SIR=1155.7 [129.8-4172.6]; $p<0.05$, respectively). We did not find any differences between the incidence rates of digestive, gynaecological and lung carcinoma between controls and the French women population, between *BRCA1/2* carriers and the French population; and between *BRCA1/2* non carriers and the French population. These results are presented in Table 1-3. Some studies have suggested that patients with familial breast cancer history are at increased risk of developing ovarian cancer compared with general population[11,12]. Our results support these findings with median follow-up of nine years. Other authors reported that women from *BRCA* mutation-negative, site specific breast cancer families were not at increased risk for ovarian cancer[3]. However, the mean follow-up of patients in this study was only 40.6 months.

Table 1: Incidence rates of second non-breast malignancies in the control population compared to the incidence in the French women population; *Incidence rates for 100,000 persons-year, **standardized by age

	France*	Controls*	SIR**	IC 95 %	p
Gynaecological	28	133.2	368.2	[74-1075.7]	NS
Ovarian	14.9	0	0	[0-846.5]	NS
Gastro-Intestinal	77.8	0	0	[0-261.3]	NS
Pulmonary	15.9	44.4	233.2	[3.1-1297.4]	NS
All	136.6	177.6	129.8	[34.9-332.4]	NS

Table 2: Incidence rates of second non-breast malignancies in BRCA1/2 non carriers compared to the incidence in the French women population; *Incidence rates for 100,000 persons-year, **standardized by age

	France*	BRCA1/2 non carriers*	SIR**	IC 95 %	p
Gynaecological	28	0	0	[0-1128.5]	NS
Ovarian	14.9	224.6	1155.7	[129.8-4172.6]	<0.05
Gastro-Intestinal	77.8	0	0	[0-639]	NS
Pulmonary	15.9	0	0	[0-2130.5]	NS
All	136.6	224.6	241.1	[48.4-704.4]	NS

Table 3: Incidence rates of second non-breast malignancies in BRCA1/2 carriers-compared to the incidence in the French women population; *Incidence rates for 100,000 persons-year, **standardized by age

	France*	BRCA1/2 carriers*	SIR**	IC 95 %	p
Gynaecological	28	0	0	[0-4768.3]	NS
Ovarian	14.9	1764.7	9640.1	[2593.6-24680.6]	<0.0001
Gastro-Intestinal	77.8	441.2	875.5	[11.44-4871]	NS
Pulmonary	15.9	0	0	[0-9294]	NS
All	136.6	2205.9	1837.5	[592.1-4288]	<0.0001

Our study confirms the conclusion of Thompson *et al.*[5], that the first site of non breast malignancies is the ovary. In spite of the homogeneity of our series and the matching of patients with their controls, the number of patients is not sufficient to make definitive conclusions. Studies of larger series of patients with longer follow-up are needed before decreeing that this specific population of patients does not need special screening for ovarian cancer. Other interesting fact showed by our study is that the patients, who present *BRCA1*/*BRCA2* mutation, have no elevated risk for cancers at sites other than the breast and ovaries. The power of our study is not enough to confirm this conclusion. We prepare another study with more patients to answer to this question.

In conclusion, after 9 year follow-up, our study showed that the rate of ovarian cancer was increased in *BRCA1/2* mutation carriers as well as in *BRCA1*/*2* non carriers compared to the general population. We also showed that these patients were not at higher risk of SNBM other than ovarian cancer. Therefore, screening for ovarian cancer is needed for both carriers and non carriers. However, large prospective screening programs are needed to evaluate the risk of ovarian cancer before offering risk-reduction strategies to women with family history but without *BRCA1* or *BRCA2* mutation. No differences have been found in the incidence rates of SNBM other than ovarian cancer between controls and the French women population, between *BRCA1*/*2* carriers, non carriers and the general population, but more statistical power is needed to confirm these results.

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