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EPIDEMIOLOGY

# Risk of second breast cancer according to estrogen receptor status and family history

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**Abstract** A recent study reported an increased risk of contralateral estrogen-negative breast cancer after a first primary estrogen-negative breast cancer. Our study aims to confirm this result and to evaluate how the risk of second breast cancer occurrence is affected by family history of breast cancer and anti-estrogen treatment. We included all 4,152 women diagnosed with breast cancer between 1995 and 2007, using data from the population-based Geneva Cancer Registry. We compared the incidence of second breast cancer among patients according to estrogen receptor (ER) status with that expected in the general population by age-period Standardized Incidence Ratios (SIRs). Among the cohort, 63 women developed second breast cancer. Patients with ER-positive first tumors had a decreased risk of second breast cancer occurrence (SIR: 0.67, 95% CI: 0.48–0.90), whereas patients with ER-negative primary tumors had an increased risk (SIR: 1.98, 95% CI: 1.19–3.09) limited to ER-negative second tumors (SIR: 7.94, 95% CI: 3.81–14.60). Patients with positive family history had a tenfold (SIR: 9.74, 95% CI: 3.57–21.12) higher risk of ER-negative second tumor which increased to nearly 50-fold (SIR: 46.18, 95% CI: 12.58–118.22) when the first tumor was ER-negative. Treatment with anti-estrogen decreased the risk of second ER-positive tumors but not ER-negative tumors. The risk of second ER-negative breast cancer is very high after a first ER-negative tumor, in particular among women with strong family history. Surveillance and prevention of second cancer occurrence should consider both ER status of the first tumor and family history.

**Keywords** Breast cancer · Estrogen receptor status · Second cancer · Family history

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## Introduction

Before the introduction of tamoxifen as treatment for hormone receptor-positive tumors, approximately 15% of breast cancer patients developed contralateral breast cancer, conferring a twofold increased risk compared with the general population [1]. An Oxford meta-analysis of clinical trials concluded that tamoxifen decreases the risk of contralateral breast cancer by 43% after 5-years of treatment [2]. However, if tamoxifen largely decreases the risk of estrogen receptor-positive (ER) tumors, several studies reported that it may increase the risk of developing ER-negative tumors [3–8]. In a recent study by Li et al. [9], use of anti-estrogen during 5 years or more was associated with a 4.4-fold increased risk of ER-negative breast cancer.

Non-Caucasian ethnicity [10]; young age at diagnosis [10–14]; positive family history of breast cancer [11, 14–17]; and lobular or medullar histology [10, 11, 14, 18] have been associated with a higher risk of contralateral breast cancer [19–23]. Recently, Kurian et al. [24] reported that breast cancer patients with both estrogen and progesterone receptor-negative tumors had higher risk of developing contralateral breast tumors, in particular hormone receptor-negative tumors. The authors did not evaluate the effect of family history of cancer nor anti-estrogen treatment.

In this study, we assess the risk of subsequent ER-positive and ER-negative contralateral tumors in breast cancer patients. In addition, we evaluated whether ER status of the first tumor, family history of breast and/or ovarian cancer, and use of anti-estrogens modified the association.

## Patients and methods

Using data from the population-based Geneva Cancer Registry, we identified 4,577 women diagnosed with unilateral first, primary invasive breast cancer between 1995 and 2007 in the Swiss canton of Geneva. After exclusion of patients with previous invasive cancer (except nonmelanoma skin cancer) ($n = 328$), breast cancer without histological confirmation ($n = 63$), breast sarcoma or lymphoma ($n = 17$), and breast cancer discovered at death ($n = 17$), the cohort included 4,152 patients. Follow-up was completed on December 31st 2007.

The Geneva Cancer Registry collects information from various sources and is considered accurate, as attested by its very low percentage (<2%) of cases recorded from death certificates only [25]. All hospitals, pathology laboratories, and private practitioners in the canton are requested to report every cancer case. Trained tumor registrars systematically extract data from medical and laboratory records, and physicians regularly receive enquiry forms to complete the missing data.

Available data include sociodemographic information, family history of cancer, tumor characteristics (coded according to the International Classification of Diseases for Oncology ICD-O) [26], hormone receptor status, and treatment during the first 6 months after diagnosis. Socioeconomic status was based on the patient's last occupation or, for the unemployed, that of the spouse. Family risk was categorized as high (at least one-first-degree relative diagnosed with breast or ovarian cancer before the age of 50 years), none (no affected first- or second-degree relative with breast or ovarian cancer), or moderate (all other known family histories). ER status was classified as positive (≥10% of tumor cells expressing receptors) or negative (<10% tumor cells expressing receptors). Women were classified as never or ever user of anti-estrogen therapy. During the study period anti-estrogen therapy consisted mainly of tamoxifen, since aromatase inhibitors were prescribed in Switzerland only from 2004. Accordingly, we defined three periods: 1995–1999 and 2000–2004, representing the time when tamoxifen was progressively being more prescribed, and 2005–2007, when prescription of aromatase inhibitors began.

### Definition of second breast cancer

Second breast cancers were defined as invasive primary breast cancer occurring in the contralateral breast at least 6 months after diagnosis of the first breast cancer. For editorial simplification we used the terms "first breast cancer" instead of first primary breast cancer and "second breast cancer" instead of second primary contralateral breast cancer.

### Statistical analysis

We used $\chi^2$ test for heterogeneity to compare patient and treatment characteristics between patients with ER-positive versus ER-negative tumors.

Person-years at risk for subsequent development of second breast cancer were computed for each woman from 6 months after the date of diagnosis of the first breast cancer to the date of diagnosis of the second breast cancer, date of death, date of loss to follow-up, or end of the study period (December 31, 2007), whichever came first. The expected number of breast cancers was calculated by multiplying the person-years at risk (stratified by 5-year intervals of age and calendar year) by the strata-specific invasive breast cancer incidence rates of the female population of the canton of Geneva. The ratio of the observed (O) to the expected (E) number of events denotes the standardized incidence ratio (SIR). This SIR represents the relative risk, adjusted for age and calendar year of developing a second breast cancer for patients diagnosed with

first breast cancer compared with women without such a diagnosis. We calculated 95% confidence intervals (95% CI) of the SIRs on the basis of the assumption that the observed number of second breast cancer followed a Poisson distribution. All *P* values are two-sided and calculated by Fisher exact test. SIRs were calculated for all second breast cancers and separately for ER-positive and ER-negative first breast cancers. Calculations of SIRs were done with the program PYRS [27].We performed stratified analyses by ER status of the first breast cancer, age, period of diagnosis, and family history. We also used multivariate Cox models to assess the independent effect of each factor and their interaction on the risk of developing a second breast cancer.

## Results

Among the 4,152 women with breast cancer, 3,335 (80.3%) had ER-positive, 620 (15%) had ER-negative, and 197 (4.7%) unknown ER tumor status (Table 1). Women with ER-negative tumors were younger and often pre-menopausal. ER-negative tumors were less frequently diagnosed following screening, more often diagnosed in advanced stages, and more often poorly differentiated. In particular, only 16.8% of ER-negative tumors were diagnosed by screening compared to 33.5% of ER-positive ones. ER status was highly correlated with progesterone receptor status and the use of anti-estrogen therapy. The proportion of ER-negative status was similar among women with highly increased, moderately increased, and no increased familial risks of breast or/and ovarian cancer.

The median follow-up period was 5 years and 2 months. The cohort yielded a total of 21,400 person-years. Between July 1995 and December 2007, 63 second breast cancer cases were diagnosed. Information on ER status of the first tumor was known for 62 of these 63 cases.

### Standardized incidence ratios

Overall, the risk of developing a second breast cancer among women diagnosed with a first breast cancer of any ER status was similar to the risk of developing a first breast cancer in the general population (Standardized Incidence Ratio SIR: 0.82; 95% CI: 0.62–1.02; $P = 0.108$) (Table 2). Patients with ER-positive first breast cancers had a significantly reduced risk of second breast cancers in general (SIR: 0.67, 95% CI: 0.48–0.90), specifically ER-positive disease (SIR: 0.55, 95% CI: 0.37–0.79). Conversely, women with an ER-negative first breast cancer had a significant increased risk of second breast cancer (SIR: 1.98, 95% CI: 1.19–3.09), in particular of second ER-negative tumors (SIR: 7.94, 95% CI: 3.81–14.60) (Table 2).

### Effect of age at diagnosis

Young women (<50 years) showed an overall increased risk of developing second breast cancer (SIR: 1.79, 95% CI: 1.08–2.80). Stratified analyses by ER status of the second breast cancer suggest that this increased risk was limited to ER-negative tumors (SIR: 4.12, 95% CI: 1.65–8.49). On the contrary, women ≥50 years old showed an overall decreased risk of second breast cancer (SIR: 0.66, 95% CI: 0.48–0.89). When stratifying by ER status of the second tumor, this lowered risk was limited to ER-positive tumors (SIR: 0.49, 95% CI: 0.32–0.71).

### Effect of period of diagnosis

The risk of second ER-positive breast cancer was around 0.60 for the three study periods (SIR: 0.63, 95% CI: 0.39–0.95 in 1995–1999; SIR: 0.56, 95% CI: 0.31–0.94 in 2000–2004, and SIR: 0.55, 95% CI: 0.07–1.99 in 2005–2007). The risk of second-ER negative breast cancer was 1.10 (95% CI: 0.40–2.39) in 1995–1999, 2.18 (95% CI: 0.94–4.29) in 2000–2004, and increased to 7.76 (95% CI: 2.11–19.87) in 2005–2007.

### Effect of anti-estrogen treatment

Overall, the use of anti-estrogens was associated with a decreased risk of second ER-positive breast cancer (SIR: 0.49, 95% CI: 0.31–0.74) and had no association with second ER-negative tumor occurrence (SIR: 1.00, 95% CI: 0.40–2.06) (Table 3). As anti-estrogens were almost exclusively prescribed to patients with ER-positive tumors (Table 1), we were unable to estimate their effect on second cancer occurrence among patients with ER-negative breast cancer.

### Effect of family history

Among women without a family history of breast and/or ovarian cancer, the risk of second breast cancer was not significantly different for neither ER-positive second breast cancer (SIR: 0.74, 95% CI: 0.50–1.05) nor ER-negative second breast cancer (SIR: 1.09, 95% CI: 0.44–2.25) (Table 4). In contrast, women with a strong family history showed a nearly tenfold higher risk of developing an ER-negative second tumor (SIR: 9.74, 95% CI: 3.57–21.12) (Table 4). Analysis by ER status of the first tumor showed that this risk was approximately 50-fold increased (SIR: 46.18, 95% CI: 12.58–118.22) when the first breast cancer was ER-negative, and not significantly increased (SIR: 3.90, 95% CI: 0.47–14.08) among women with ER-positive first breast cancer (Table 5).

**Table 1** Patient, tumor, and treatment characteristics according to ER status of the first breast cancer

| Characteristics | ER status | | | | | | *P*-values* |
|---|---|---|---|---|---|---|---|
| | Positive | | Negative | | Unknown | | |
| | *N* | % | *N* | % | *N* | % | |
| *N* | 3335 | 80.3 | 620 | 15.0 | 197 | 4.7 | |
| Person-years of observation | 17542 | | 2903 | | 953 | | |
| Mean age (SD) | 60.4 | (12.9) | 56.8 | (14.3) | 65.9 | (15.9) | |
| Age category | | | | | | | 0.000 |
| <40 | 138 | 4.1 | 69 | 11.1 | 4 | 2.0 | |
| 40–49 | 572 | 17.2 | 139 | 22.4 | 36 | 18.3 | |
| 50–59 | 941 | 28.2 | 163 | 26.3 | 35 | 17.8 | |
| 60–69 | 874 | 26.2 | 116 | 18.7 | 41 | 20.8 | |
| 70–79 | 528 | 15.8 | 95 | 15.3 | 32 | 16.2 | |
| ≥80 | 282 | 8.5 | 38 | 6.1 | 49 | 24.9 | |
| Menopausal status | | | | | | | 0.000 |
| Pre- and peri-menopausal | 830 | 24.9 | 228 | 36.8 | 34 | 17.3 | |
| Post-menopausal | 2471 | 74.1 | 385 | 62.1 | 142 | 72.1 | |
| Unknown | 34 | 1.0 | 7 | 1.1 | 21 | 10.7 | |
| Social class | | | | | | | 0.138 |
| High | 490 | 14.7 | 90 | 14.5 | 28 | 14.2 | |
| Middle | 1699 | 50.9 | 321 | 51.8 | 82 | 41.6 | |
| Low | 514 | 15.4 | 112 | 18.1 | 33 | 16.8 | |
| Unknown | 632 | 19.0 | 97 | 15.6 | 54 | 27.4 | |
| Family risk | | | | | | | 0.862 |
| Low | 2170 | 65.1 | 413 | 66.6 | 105 | 53.3 | |
| Moderate | 752 | 22.5 | 133 | 21.5 | 27 | 13.7 | |
| High | 218 | 6.5 | 37 | 6.0 | 5 | 2.5 | |
| Unknown | 195 | 5.8 | 37 | 6.0 | 60 | 30.5 | |
| Period of diagnosis | | | | | | | 0.002 |
| 1995–1999 | 1090 | 32.7 | 248 | 40.0 | 134 | 68.0 | |
| 2000–2004 | 1441 | 43.2 | 238 | 38.4 | 53 | 26.9 | |
| 2005–2007 | 804 | 24.1 | 134 | 21.6 | 10 | 5.1 | |
| Method of detection | | | | | | | 0.000 |
| Screening | 1116 | 33.5 | 104 | 16.8 | 22 | 11.2 | |
| Clinical examination | 389 | 11.7 | 52 | 8.4 | 17 | 8.6 | |
| BSE | 1279 | 38.4 | 325 | 52.4 | 46 | 23.4 | |
| Others | 551 | 16.5 | 139 | 22.4 | 112 | 56.9 | |
| Stage | | | | | | | 0.000 |
| I | 1415 | 42.4 | 173 | 27.9 | 42 | 21.3 | |
| II | 1386 | 41.6 | 270 | 43.5 | 63 | 32.0 | |
| III | 312 | 9.4 | 106 | 17.1 | 16 | 8.1 | |
| IV | 131 | 3.9 | 45 | 7.3 | 31 | 15.7 | |
| Unknown | 91 | 2.7 | 26 | 4.2 | 45 | 22.8 | |
| Histological subtype | | | | | | | 0.000 |
| Ductal | 2618 | 78.5 | 525 | 84.7 | 104 | 52.8 | |
| Lobular | 530 | 15.9 | 23 | 3.7 | 20 | 10.2 | |
| Other | 187 | 5.6 | 72 | 11.6 | 73 | 37.1 | |
| Differentiation | | | | | | | 0.000 |
| Good | 1112 | 33.3 | 30 | 4.8 | 32 | 16.2 | |
| Moderate | 1618 | 48.5 | 180 | 29.0 | 30 | 15.2 | |

**Table 1** continued

| Characteristics | ER status | | | | | | *P*-values* |
|---|---|---|---|---|---|---|---|
| | Positive | | Negative | | Unknown | | |
| | *N* | % | *N* | % | *N* | % | |
| Poor | 446 | 13.4 | 359 | 57.9 | 41 | 20.8 | |
| Unknown | 159 | 4.8 | 51 | 8.2 | 94 | 47.7 | |
| Progesterone receptor status | | | | | | | 0.000 |
| Positive | 2682 | 80.4 | 54 | 8.7 | 1 | 0.5 | |
| Negative | 651 | 19.5 | 566 | 91.3 | 5 | 2.5 | |
| Unknown | 2 | 0.1 | 0 | | 191 | 97.0 | |
| Radiotherapy | | | | | | | 0.957 |
| No | 821 | 24.6 | 152 | 24.5 | 144 | 73.1 | |
| Yes | 2514 | 75.4 | 468 | 75.5 | 53 | 26.9 | |
| Surgery | | | | | | | 0.353 |
| No | 239 | 7.2 | 51 | 8.2 | 96 | 48.7 | |
| Yes | 3096 | 92.8 | 569 | 91.8 | 101 | 51.3 | |
| Anti-estrogen | | | | | | | 0.000 |
| No | 499 | 15.0 | 551 | 88.9 | 119 | 60.4 | |
| Yes | 2836 | 85.0 | 69 | 11.1 | 78 | 39.6 | |
| Chemotherapy | | | | | | | 0.000 |
| No | 2160 | 64.8 | 160 | 25.8 | 151 | 76.6 | |
| Yes | 1175 | 35.2 | 460 | 74.2 | 46 | 23.4 | |

*ER* estrogen receptor; *BSE* breast self-examination

* $\chi^2$ of heterogeneity between patients with ER-positive and ER-negative tumors

**Table 2** Risk of ER-positive or ER-negative second breast cancer occurrence according to ER status of the first tumor

| | Women at risk *N* | Observed cases *N* | Expected cases *N* | SIR[a] | (95% CI) | *P*-values | Incidence rates[b] |
|---|---|---|---|---|---|---|---|
| All first breast cancers | 4152 | | | | | | |
| All second breast cancers | | 63 | 76.83 | 0.82 | (0.62–1.02) | NS | 294.41 |
| Second ER+ | | 38 | 63.33 | 0.60 | (0.42–0.82) | <0.05 | 177.58 |
| Second ER− | | 18 | 9.63 | 1.87 | (1.11–2.96) | <0.05 | 84.12 |
| Second ER unknown | | 7 | 4.17 | 1.68 | (0.67–3.46) | NS | 32.71 |
| First ER-positive | 3335 | | | | | | |
| All second breast cancers | | 43 | 64.18 | 0.67 | (0.48–0.90) | <0.05 | 245.12 |
| Second ER+ | | 29 | 52.73 | 0.55 | (0.37–0.79) | <0.05 | 165.31 |
| Second ER− | | 8 | 7.92 | 1.01 | (0.44–1.99) | NS | 45.60 |
| Second ER-unknown | | 6 | 3.37 | 1.78 | (0.65–3.86) | NS | 34.20 |
| First ER-negative | 620 | | | | | | |
| All second breast cancers | | 19 | 9.60 | 1.98 | (1.19–3.09) | <0.05 | 654.46 |
| Second ER+ | | 8 | 7.84 | 1.02 | (0.44–2.01) | NS | 275.56 |
| Second ER− | | 10 | 1.26 | 7.94 | (3.81–14.60) | <0.05 | 344.45 |
| Second ER-unknown | | 1 | 0.50 | 2.02 | (0.06–11.25) | NS | 34.45 |

[a] Age period standardized incidence ratio

[b] Rates are adjusted for age, using as standard the 5-year age distribution of the Geneva female resident population; rates are per 100'000 person-years

*ER* estrogen receptor, *CI* confidence interval, *NS* not significant

## Cox models

The results of the multivariate analysis with Cox model simultaneously adjusted for estrogen receptor, age, period, anti-estrogen therapy, and family history are presented in Table 6.

None of these factors had an impact on the risk of developing an ER-positive second breast cancer. ER-negative status, most recent period of diagnosis, and strong family history were associated with an increased risk of second ER-negative breast cancer. In particular, the risk (Adjusted Hazard Ratio) was 13.33 (95% CI: 2.52–70.61) for patients diagnosed in 2005–2007 versus 1995–1999, and 9.16 (95% CI: 3.06–27.42) for patients with strong versus no family history risk of breast or ovarian cancer. None of the interaction tests was significant.

**Table 3** Risk of ER-positive or ER-negative second breast cancer according to anti-estrogen treatment use for the first tumor

| | Second breast cancer | | | | | | |
|---|---|---|---|---|---|---|---|
| | Women at risk *N* | Observed cases *N* | Expected cases *N* | SIR[a] | (95% CI) | *P*-values | Incidence rates[b] |
| With anti-estrogen use | 2983 | | | | | | |
| All second breast cancers | | 33 | 56.90 | 0.58 | (0.40–0.81) | <0.05 | 215.21 |
| Second ER+ | | 23 | 46.94 | 0.49 | (0.31–0.74) | <0.05 | 149.99 |
| Second ER− | | 7 | 7.00 | 1.00 | (0.40–2.06) | NS | 45.65 |
| Second ER-unknown | | 3 | 2.94 | 1.02 | (0.21–2.98) | NS | 19.56 |
| Without anti-estrogen use | 1169 | | | | | | |
| All second breast cancers | | 30 | 20.55 | 1.46 | (0.99–1.46) | NS | 494.66 |
| Second ER+ | | 15 | 16.67 | 0.90 | (0.50–1.48) | NS | 247.33 |
| Second ER− | | 11 | 2.65 | 4.15 | (2.07–7.42) | <0.05 | 181.38 |
| Second ER-unknown | | 4 | 1.23 | 3.26 | (0.89–8.35) | NS | 65.95 |

[a] Age period standardized incidence ratio

[b] Rates are adjusted for age, using as standard the 5-year age distribution of the Geneva female resident population; rates are per 100'000 person-years

*ER* estrogen receptor, *CI* confidence interval, *NS* not significant

**Table 4** Risk of ER-positive or ER-negative second breast cancer according to family history

| | Second breast cancer | | | | | | |
|---|---|---|---|---|---|---|---|
| | Women at risk *N* | Observed cases *N* | Expected cases *N* | SIR[a] | (95% CI) | *P* value | Incidence rates[b] |
| Family history | | | | | | | |
| None | 2688 | | | | | | |
| All second breast cancers | | 41 | 51.25 | 0.80 | (0.57–1.09) | NS | 289.29 |
| Second ER+ | | 31 | 41.89 | 0.74 | (0.50–1.05) | NS | 218.73 |
| Second ER− | | 7 | 6.42 | 1.09 | (0.44–2.25) | NS | 49.39 |
| Second ER-unknown | | 3 | 2.75 | 1.09 | (0.23–3.19) | NS | 21.17 |
| Moderate | 912 | | | | | | |
| All second breast cancers | | 11 | 17.46 | 0.63 | (0.31–1.13) | NS | 224.73 |
| Second ER+ | | 4 | 14.29 | 0.28 | (0.08–0.72) | <0.05 | 81.72 |
| Second ER− | | 4 | 2.22 | 1.80 | (0.49–4.61) | NS | 81.72 |
| Second ER-unknown | | 3 | 0.87 | 3.45 | (0.71–10.09) | NS | 61.29 |
| Strong | 260 | | | | | | |
| All second breast cancers | | 9 | 4.81 | 1.87 | (0.86–3.55) | NS | 671.38 |
| Second ER+ | | 3 | 4 | 0.75 | (0.16–2.19) | NS | 223.79 |
| Second ER− | | 6 | 0.62 | 9.74 | (3.57–21.12) | <0.05 | 447.59 |
| Second ER-unknown | | 0 | 0.22 | – | – | – | – |
| Unknown | 292 | | | | | | |
| All second breast cancers | | 2 | 3.64 | 0.55 | (0.07–1.99) | NS | 201.79 |
| Second ER+ | | 0 | 2.9 | – | – | – | – |
| Second ER− | | 1 | 0.41 | 2.46 | (0.07–13.70) | NS | 100.89 |
| Second ER-unknown | | 1 | 0.32 | 3.11 | (0.09–17.32) | NS | 100.89 |

[a] Age period standardized incidence ratio

[b] Rates are adjusted for age, using as standard the 5-year age distribution of the Geneva female resident population; rates are per 100'000 person-years

*ER* estrogen receptor, *CI* confidence interval, *NS* not significant

## Discussion

This study shows that the risk of developing a second contralateral tumor after breast cancer is modified by ER status of the first primary tumor, period of diagnosis, and family history of breast and or ovarian cancer. In addition, we showed that women with ER-positive tumors have a decreased risk of developing a second ER-positive tumor, whereas patients whose first tumor is ER-negative have an increased risk of developing a second ER-negative tumor. A strong family history of breast and/or ovarian cancer further increases the risk of developing a second ER-negative tumor. In particular, patients with both ER-negative tumors and strong family history presented a very high risk of developing a second ER-negative tumor.

A major limitation of our study is the lack of central pathological reviews of the breast tumors. However, in Geneva, there are only three laboratories of cyto-

**Table 5** Risk of second breast cancer according to ER status of the first tumor and family history stratified by ER status of the second tumor

| Strong family history | ER status of the first breast cancer | | | | | |
|---|---|---|---|---|---|---|
| | Positive | | Negative | | Unknown | |
| | Observed/ expected *N* | SIR[a] (95% CI) | Observed/ expected *N* | SIR[a] (95% CI) | Observed/ expected *N* | SIR[a] (95% CI) |
| All second breast cancers | | | | | | |
| No | 39/60.0 | 0.65 (0.46–0.89)* | 14/8.92 | 1.57 (0.86–2.63) | 1/3.33 | 0.30 (0.01–1.67) |
| Yes | 4/4.04 | 0.99 (0.27–2.53) | 5/0.65 | 7.67 (2.49–17.90)* | 0/0.14 | – |
| Second breast cancer with ER-positive receptors | | | | | | |
| No | 27/49.09 | 0.55 (0.36–0.80)* | 7/7.29 | 0.96 (0.39–1.98) | 1/2.63 | 0.38 (0.01–2.12) |
| Yes | 2/3.33 | 0.60 (0.07–2.17) | 1/0.53 | 1.87 (0.06–10.42) | 0/11.0 | – |
| Second breast cancer with ER-negative receptors | | | | | | |
| No | 6/7.41 | 0.81 (0.30–1.76) | 6/1.17 | 5.12 (1.88–11.10) | 0/0.41 | – |
| Yes | 2/0.51 | 3.90 (0.47–14.08) | 4/0.09 | 46.18 (12.58–118.22)* | 0/0.02 | – |

[a] Age period standardized incidence ratio; * $P < 0.05$; *ER* estrogen receptor, *CI* confidence interval

**Table 6** Independent effect of ER status of the first tumor, age, period, family history, and anti-estrogen use on second breast cancer occurrence

| Characteristics | Adjusted hazard ratio[a] (95% CI) of second breast cancer occurrence | | |
|---|---|---|---|
| | ER+ (37 events) | ER− (18 events) | All ER (62 events) |
| ER status of first tumor | | | |
| Positive | 1 (reference) | 1 (reference) | 1 (reference) |
| Negative | 1.22 (0.46–3.25) | 5.07 (1.21–21.28)* | 1.66 (0.82–3.36) |
| Age (years) | | | |
| ≥50 | 1 (reference) | 1 (reference) | 1 (reference) |
| <50 | 1.14 (0.55–2.39) | 1.76 (0.67–4.61) | 1.17 (0.67–2.05) |
| Period | | | |
| 1995–1999 | 1 (reference) | 1 (reference) | 1 (reference) |
| 2000–2004 | 1.09 (0.52–2.29) | 3.03 (0.83–11.0) | 1.49 (0.82–2.72) |
| 2005–2007 | 1.60 (0.33–7.89) | 13.33 (2.52–70.61)** | 4.01 (1.52–10.57)** |
| Family history | | | |
| None | 1 (reference) | 1 (reference) | 1 (reference) |
| Moderate | 0.38 (0.14–1.09) | 1.63 (0.48–5.59) | 0.80 (0.41–1.57) |
| Strong | 1.08 (0.33–3.55) | 9.16 (3.06–27.42)*** | 2.46 (1.19–5.08)* |
| Unknown | – | 2.20 (0.26–18.41) | 0.77 (0.18–3.25) |
| Anti-estrogen use | | | |
| No | 1 (reference) | 1 (reference) | 1 (reference) |
| Yes | 0.66 (0.28–1.55) | 0.56 (0.13–2.48) | 0.51 (0.26–0.99)* |

[a] Cox model adjusted for all variables in the table

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.001$

*ER* estrogen receptor; *CI* confidence interval

histopathology using identical quality-controlled ligand-binding methods for the determination of receptors. Another limitation of our study is the small number of second breast cancers, particularly in stratified analysis by ER status of the first tumor and family history. Therefore, further sub-classification into ER-positive and ER-negative second tumors yields estimates with wide confidence intervals. The interpretation of the risk specific to second ER-positive and second ER-negative tumors according to the ER status of the first tumor should be made in light of the low number of cases. Another shortcoming of the study is the lack of information on the duration of anti-estrogen treatment. The strength of this study is its population-based design with prospective collection of patient and tumor characteristics. Information on family history is accurate as attested by its high sensitivity and specificity (98 and 97%, respectively) in the population under study [28].

Our results are in concordance with the recent study by Kurian et al. [24] who reported a 9.8-fold increased risk of developing a second ER-negative tumor. Of note, in their study, the overall risk of developing a second breast cancer after a first hormone receptor-positive tumor was higher in

breast cancer patients than in the general population (SIR: 2.22, 95% CI: 2.15–2.29) whereas in our study, using the same methodology, the overall risk of developing a second breast cancer after an ER-positive tumor was lower (SIR: 0.82, 95% CI: 0.62–1.02). Exclusion of 18% of patients with unknown data on ER status in the SEER study or differences in the prevalence of tamoxifen use could partly explain this difference.

The decreased risk of overall second breast cancer is likely linked to the use of anti-estrogens among women with ER-positive tumors. In Geneva, as compared with the general population, the risk of second breast cancer occurrence before the tamoxifen era in 1970–1980 was 1.58 (95% CI: 1.28–1.88) and decreased to 0.82 (95% CI: 0.62–1.02) during the study period. Our results confirm the decrease of second breast cancer occurrence observed in clinical trials on tamoxifen use [2].

However, as reported in previous publications, this study also shows that tamoxifen has no effect on ER-negative second tumor occurrence [6, 13]. A recent article by Li et al. [9] even reported that use of tamoxifen for 5 or more years increases the risk of second ER-negative breast cancer. We did not observe such an effect in Geneva, where the standard protocol used to be to prescribe tamoxifen for 5 years.

As previously observed, young age at first breast cancer diagnosis increases the risk of second breast cancer [1]. Our study shows that young women (<50 years) with breast cancer are at increased risk of developing ER-negative but not ER-positive second breast cancer. However, in multivariate analysis, age at diagnosis was no longer significantly associated with second tumor occurrence.

A rather remarkable finding is the very strong risk of developing second ER-negative breast cancer among patients with strong family history, particularly when the first tumor is ER-negative. A recent study reported that breast cancer patients with *BRCA1* or *BRCA2* mutations presented a 47% cumulative risk of developing contralateral breast cancer without considering ER status neither of the first nor of the second breast tumor [29]. ER-positive and ER-negative breast cancers most probably differ in terms of etiology and natural history. A recent study among breast cancer patients diagnosed before the age of 40 years reported that use of contraceptive pills was associated with a fivefold increased risk of triple negative breast cancer but had no effect on cancers with other pathological profiles [30].

Our study also shows that the risk of second ER-negative breast cancer is particularly high for patients diagnosed during the last study period, i.e., when aromatase inhibitors treatment increased. In 1995–1999, 63% of women with breast cancer included in the study received tamoxifen and 0% anti-aromatase. The corresponding proportions were 71 and 7% in 2000–2004, and 38 and 35% in 2005–2007. We therefore hypothesize that the risk of ER-negative cancer putatively linked to anti-aromatase could in fact be greater than with tamoxifen.

Sensitivity of mammography is lower for ER-negative breast cancers which are more frequently interval cancers [31]. Our results found that ER-negative cancers are less frequently detected by screening than ER-positive tumors and diagnosed at more advanced stages. It is also well documented that ER-negative tumors are more likely to be poorly differentiated [32] as observed in this study. ER status is a strong predictive factor by which we identify patients who benefit from endocrine therapy. Women with ER-negative tumors need adjuvant chemotherapy [33–35].

This study provides additional evidence on differences between ER-positive and ER-negative breast cancers not only in presentation, prognosis, and treatment but also in etiology and natural history. It also provides clinicians with information in establishing the follow-up of breast cancer patients. Surveillance of second cancer occurrence should be adjusted according to both ER status of the primary breast cancer and family history of the patient. In particular, specific preventive interventions such as chemoprevention or prophylactic surgery should be considered for women with both positive family history and ER-negative first tumors. The putative increased risk of second ER-negative tumor occurrence among patients treated with anti-aromatase should be carefully evaluated.

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