

Family history of breast or ovarian cancer modifies the risk of secondary leukemia after breast cancer: Results from a population-based study

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We evaluated the impact of a family history of breast/ovarian cancer on the risk of secondary leukemia following breast cancer. At the Geneva cancer registry, we identified 4,397 patients diagnosed with invasive breast cancer between 1990 and 2004. Patients were followed up for leukemia until the end of 2005. Family history was categorized as positive in patients with ≥ 1 first- or second-degree relative with breast/ovarian cancer. We compared leukemia rates in patients with positive and negative family histories with those expected in the general population, generating standardized incidence ratios (SIRs). With Cox regression analysis, we calculated adjusted risks of secondary leukemia in patients with familial risks compared to those without it. Breast cancer patients had a significantly increased risk of secondary acute leukemia (SIR 3.2, 95% CI: 1.2–6.9) but not of chronic leukemia (SIR 1.6, 95% CI: 0.6–3.5). Among patients with a positive family history ($n = 1,125$, 25.6%), the SIRs were 5.7 (95% CI: 1.2–16.6) for acute and 5.2 (95% CI: 1.4–13.3) for chronic leukemia. Among breast cancer patients, family history was independently associated with leukemia [adjusted hazard ratio (HR_{adj}) of 3.2, 95% CI: 1.1–9.2, among patient with vs. without family history]. The effect of family history was stronger for chronic leukemia (HR_{adj}: 11.6, 95% CI 1.3–104.7) than for acute leukemia (HR_{adj} 1.6, 95% CI: 0.4–6.6). Breast cancer patients with a family history of breast/ovarian have an increased risk of secondary leukemia, both compared to the general population as well as to breast cancer patients without family histories. This excess risk is largely due to the increased risk of secondary chronic leukemia.

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The risk of secondary leukemia following treatment for breast cancer has been well established.^{1–4} Modifiers of this risk include increasing age and exposure to radiotherapy as well as certain types of chemotherapy.^{5–7} Most studies reported only increased risks of acute myeloid leukemia following breast cancer, but a recent large, population-based study has shown that breast cancer patients are at increased risk of developing acute lymphoblastic leukemia and chronic myeloid leukemia as well.¹

A family history of leukemia or other hematologic malignancies is not considered as a major risk factor for leukemia,^{8–10} except for chronic lymphocytic leukemia.¹¹ There have been some reports of breast cancer and leukemia clustering in families, in particular, in the context of some hereditary cancer syndromes like ataxia-telangiectasia and Li-Fraumeni syndrome.^{10,12} In addition, Rauscher *et al.* reported that adults, whose sisters had been diagnosed with breast cancer, were at 1.8–3.3 times increased risk of developing acute leukemia.¹³

Although the excess absolute risk of secondary leukemia following breast cancer is rather low—around 9 extra cases per 100,000 person years—and the individual risk of developing leukemia following breast cancer is decreasing,¹ the overall the burden of this serious complication may actually rise. The increasing incidence of breast cancer in combination with improving survival rates leads to increasing numbers of women at risk of leukemia following breast cancer. The aging of the population may also

contribute to increasing numbers of leukemia following breast cancer, since some studies have indicated that the risk of leukemia following breast cancer is highest among women who developed breast cancer at an older age.² Finally, the number of patients managed with breast conserving treatment, including lumpectomy and radiotherapy, is still on the rise, leading to increasing number of patients exposed to ionizing radiation and therefore at increased risk of leukemia.

For this reason, it would be useful to identify additional risk factors for leukemia after breast cancer, in order to be able to better predict which women will develop this often highly fatal disease. In this study, we evaluated whether the risk of secondary leukemia after breast cancer is modified by family history of breast/ovarian cancer.

Methods

We used information from the population-based Geneva Cancer Registry, which records all incident cancers occurring in the population of the Geneva canton (~420,000 inhabitants) since 1970. It collects information from various sources and is considered accurate, as attested by its very low percentage (<2%) of cases recorded from death certificates only.¹⁴ All hospitals, pathology laboratories and private practitioners in the canton are requested to report all cancer cases. Trained tumor registrars systematically abstract data from medical and laboratory records. Physicians regularly receive enquiry forms to complete missing clinical and therapeutic data.

Recorded data include sociodemographic information, tumor characteristics coded according to the International Classification of Diseases for Oncology¹⁵ and treatment given during the first 6 months after diagnosis. The Registry staff regularly assess survival, taking as reference date the date of confirmation of diagnosis or the date of hospitalization (if it preceded the diagnosis and was related to the disease). In addition to passive follow-up (standard examination of death certificates and hospital records), active follow-up is performed yearly using the files of the Cantonal Population Office (office in charge of the registration of the resident population). Cause of death is taken from clinical files.

In the current study, we included resident patients diagnosed with invasive breast cancer between 1990 and 2004. We limited our study to this period, since for these years information on family history of cancer was available. Family history of breast and/or ovarian cancer was obtained from the Familial Breast Cancer Registry. This unit of the Geneva Cancer Registry was set up in

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