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Contralateral breast cancer in patients with ductal carcinoma in situ and invasive breast cancer in the Netherlands

D. Giardiello[1,2], I. Kramer[1], M.J. Hooning[3], M. Hauptmann[4,5], E. Lips[1], E. Sawley[6], A. Thompson[7], L. de Munck[8], S. Siesling[8,9], J. Wesseling[1,10], E.W. Steyerberg[2,11], M.K. Schmidt[1,12]. *[1]The Netherlands Cancer Institute, Molecular Pathology, Amsterdam, Netherlands; [2]Leiden University Medical Center, Biomedical Data Sciences, Leiden, Netherlands; [3]Erasmus MC Cancer Institute, Medical Oncology, Family Cancer Clinic, Rotterdam, Netherlands; [4]Brandenburg Medical School, Institute of Biostatistics and Registry Research, Neuruppin, Germany; [5]The Netherlands Cancer Institute, Epidemiology and Biostatistics, Amsterdam, Netherlands; [6]Kings College London, School of Cancer & Pharmaceutical Science, Guys Cancer Centre, London, United Kingdom; [7]Baylor College of Medicine, Surgical Oncology, Houston, USA; [8]Netherlands Comprehensive Cancer Organisation, Research and Development, Utrecht, Netherlands; [9]University of Twente, Health Technology and Services Research, Technical Medical Centre, Enschede, Netherlands; [10]Leiden University Medical Center, Pathology, Leiden, Netherlands; [11]Erasmus MC Cancer Institute, Public Health, Rotterdam, Netherlands; [12]Leiden University Medical Center, Clinical Genetics, Leiden, Netherlands*

Background: The cumulative incidence of invasive contralateral breast cancer (CBC) for patients with first invasive breast cancer (BC) is approximately 0.4% per year. Less is known about CBC risk in patients with ductal carcinoma in situ (DCIS). We aimed to assess the CBC risk in patients with first DCIS compared to those with invasive BC, taking age, screening period, and (neo) adjuvant systemic therapy into account.

Material and Methods: From the nationwide, population-based Netherlands Cancer Registry, all women diagnosed with first DCIS (N = 28,003) or first invasive BC stage I-III (N = 275,836) between 1989 and 2017 were selected. Follow-up for second tumors and death was complete until 2018. Cumulative incidences, for invasive metachronous CBC (diagnosed ≥3 months after the first diagnosis) was calculated accounting for invasive ipsilateral BC, in situ CBC and mortality as competing risks. Cox regression models were performed to calculate the risk to develop invasive CBC for women with DCIS compared to women with BC using hazard ratios (HRs). Discrimination (c-statistic) of multivariable Cox regression models was calculated to assess the ability of the predictors routinely available in clinical practice for women with BC or DCIS to predict CBC risk.

Results: During a median follow-up of 7.8 years, 1,334 invasive CBC events occurred among DCIS patients and 12,821 among BC patients. The 10-year cumulative incidence was 4.8% in DCIS patients and 4.0% in BC patients (HR: 1.08; 95% confidence interval [CI]:1.01–1.14). The CBC risk was lower in patients with DCIS compared to patients with stage I BC not treated with (neo)adjuvant systemic therapy (N = 86,481, HR:0.87; 95% CI: 0.82–0.92). For patients at first diagnosis ≥50 years between 1989 and 1998 (implementation phase national screening program), the 10-year cumulative CBC incidences were 4.3% and 4.1% for DCIS and BC patients, respectively, and 5.1% and 3.9% between 1999 and 2017 (full screening coverage for women 50–75 years) (HR:1.18; 95% CI:1.10–1.26). For patients <50 years and diagnosed between 1989 and 1998 (no systemic treatment for part of lymph node negative breast cancers according to national guidelines), the 10-year cumulative CBC incidences were 4.6% and 5.5% for DCIS and BC patients, respectively, and 4.7% and 3.5% in 1999–2017 (HR: 1.20; 95% CI: 1.06–1.37). In the multivariable model, the c-statistic was 0.53 for patients with DCIS and 0.65 for BC patients.

Conclusions: We observed a higher CBC risk in patients with DCIS compared to invasive BC, which may be largely explained by different treatment strategies, especially systemic therapies. Overall CBC risk is low and difficult to predict especially in patients with DCIS. Improved individualized CBC risk prediction may be as important for patients with DCIS as for patients with invasive BC.

No conflict of interest.

CLINICAL SCIENCE SYMPOSIUM

Early Breast Cancer and Germline Gene Panel Results: Help!

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Genome wide association study of acute radiation toxicity and quality of life in breast cancer patients – results from the REQUITE cohort study

T. Rattay[1], C.D. Veal[2], D. Azria[3], J. Chang-Claude[4], S. Davidson[5], A. Dunning[6], D. de Ruysscher[7], L. Fachal[6], S. Gutierrez-Enriquez[8], P. Lambin[9], T. Rancati[10], B.S. Rosenstein[11], P. Seibold[4], E. Sperk[12], R.P. Symonds[1], A. Vega[13], L. Veldeman[14], A.J. Webb[2], C.M.L. West[15], C.J. Talbot[2], REQUITE Study Group. *[1]University of Leicester, Leicester Cancer Research Centre, Leicester, United Kingdom; [2]University of Leicester, Genetics and Genome Biology, Leicester, United Kingdom; [3]University of Montpellier, Radiation Oncology, Montpellier, France; [4]German Cancer Research Center DKFZ, Genetic Epidemiology, Division of Cancer Epidemiology, Heidelberg, Germany; [5]The Christie Hospital NHS Foundation Trust, Clinical Oncology, Manchester, United Kingdom; [6]University of Cambridge, Centre for Cancer Genetic Epidemiology, Cambridge, United Kingdom; [7]KU Leuven, Radiation Oncology, Leuven, Belgium; [8]Vall d' Hebron Institute of Oncology, Hereditary Cancer Genetics Group, Barcelona, Spain; [9]MAASTRO Clinic, Department of Precision Medicine, Maastricht, Netherlands; [10]Fondazione IRCCS Istituto Nazionale dei Tumori, Prostate Cancer Program, Milan, Italy; [11]Icahn School of Medicine at Mount Sinai, Radiation Oncology, New York, USA; [12]Universitaetsmedizin Mannheim, Radiation Oncology, Mannheim, Germany; [13]Fundacion Publica Galega Medicina Xenomica, Medical Genetics Group, Santiago de Compostella, Spain; [14]Universiteit Ghent, Radiation Oncology, Ghent, Belgium; [15]University of Manchester, Division of Cancer Sciences, Manchester, United Kingdom*

Background: Around a quarter of breast cancer patients treated by surgery and radiotherapy experience clinically significant toxicity, which may adversely affect breast cosmesis and quality of life (QoL). If patients at high risk of toxicity could be identified at diagnosis, this could be taken into account when discussing treatment options. This study was designed to identify common single nucleotide polymorphisms (SNPs) associated with acute radiation toxicity and change in QoL on completion of radiotherapy.

Methods: A genome-wide association study (GWAS) was performed in 1,838 breast cancer patients with complete clinical, treatment and toxicity data, recruited following breast-conserving surgery across eight centres in Europe and North America into the REQUITE prospective cohort study (www.requite.eu). Toxicity (CTCAE v4.0) and QoL (EORTC-QLQ-C30 and -B23) data were collected at baseline and on completion of radiotherapy. All patients were genotyped using Illumina OncoArrays. Datasets were imputed according to methods used by the OncoArray Network. A total of 7,409.901 SNP variants with minor allele frequency >0.05 were tested for association with the residuals of acute toxicity endpoints and worsening QoL (≥10 point change from baseline, dichotomised) adjusted for clinical and treatment co-variates. Worsening QoL was also adjusted for toxicity.

Results: By the end of radiotherapy, 20.8% of patients experienced ≥grade 2 erythema, 31.6% ≥grade 1 oedema, and 9.1% acute ulceration (skin breakdown). Overall QoL, fatigue, pain, and breast symptoms worsened significantly compared to baseline. Acute erythema was associated with the Chr1 rs631134 variant, 1 kb upstream of *PLA2G2F* (phospholipase A2 Group IIF, known to affect acute skin inflammation, $p = 1.89 \times 10^{-8}$). Acute ulceration was associated with the Chr 9 rs12554549 *PTPN3* intronic variant (protein tyrosine phosphatase non-receptor type 3, $p = 2.67 \times 10^{-8}$). Several previously significant SNP associations with toxicity were validated at the nominal 0.05 level in this cohort. Quantile-quantile plots for association with worsening QoL showed more associations above the $p < 5 \times 10^{-5}$ level than expected by chance. The strongest signal was for worsening arm symptoms and the Chr 11 rs4757774 variant, 5 kb upstream of *E2F8* (E2F transcription factor 8 transcript variant, involved in regulating cell cycle gene expression, $p = 5.66 \times 10^{-8}$).

Conclusions: The results of the largest GWAS of acute breast radiation toxicity to date can be used to develop clinical predictive risk models for toxicity and change in QoL after breast surgery and radiotherapy. This has the potential to provide clinicians with important information when planning breast cancer treatment, in order to reduce side-effects and optimise quality of life.

No conflict of interest.

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Recommendations from the European Commission Initiative on Breast Cancer on multigene tests to guide the use of adjuvant chemotherapy in patients who have hormone receptor positive, HER-2 negative, lymph node negative or up to 3 lymph nodes positive invasive breast cancer

P. Giorgi Rossi[1], A. Lebeau[2], C. Canelo-Aybar[3], M.C. Posso Rivera[3], D. Rigau Comas[3], C. Quinn[4], P. Alonso Coello[3], H. McGarrigle[5], S. Warman[6], M. Broeders[7], S. Duffy[8], M.W. Langendam[9], A. Gräwingholt[10], M. Follmann[11], Z. Saz-Parkinson[12], H. Schünemann[13], for the Guidelines Development Group European Commission Initiative on