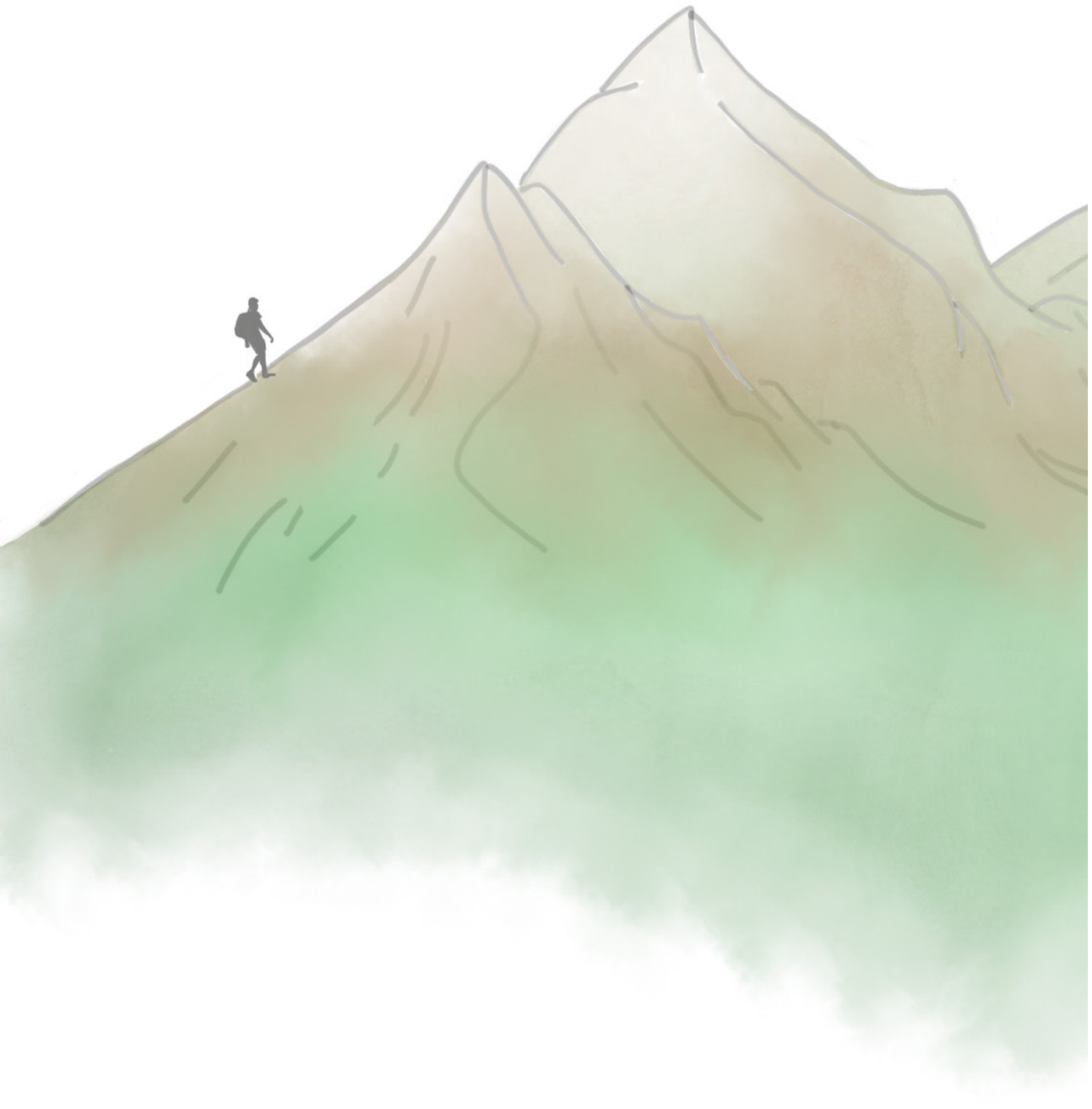
Prediction of contralateral breast cancer: statistical aspects and prediction performance

Giardiello, D.



Chapter 1

Introduction

INTRODUCTION

Breast cancer: developments and contemporary challenges

Breast cancer is the most common cancer in women in the world[1]. While the incidence of breast cancer has increased over the years, survival after breast cancer diagnosis has improved in the last 50 years due to earlier detection and advanced treatment modalities; for example, in the Netherlands, 10-year survival of first primary breast cancer approximately improved by almost 40% from 39% in 1961 to 76% in 2010[2,3]. As a consequence, breast cancer survivors may have substantial remaining lifetime to develop other cancers.

Breast cancer survivors are more likely to develop a new primary tumor in the opposite breast (defined as contralateral breast cancer) compared to healthy women to develop a first primary breast cancer[4-8]. Contralateral breast cancer is one of the biggest threats among breast cancer survivors: for example, in the Netherlands and in the United States contralateral breast cancer is the most common second primary cancer among women diagnosed with invasive breast cancer, accounting for 40-50% of all new second cancers[9,10]. About 5 out of 100 patients with invasive breast cancer will develop a contralateral breast cancer within 10 years since the diagnosis of the first primary breast cancer (10-year cumulative incidence between 4-7%, Figure 1)[11,12]. In addition, contralateral breast cancer patients have worse prognosis compared to patients with unilateral breast cancer[13-16]. Little is known about contralateral breast cancer among patients diagnosed with in situ breast cancer, a potential pre-invasive cancer occurring typically in the cell of milk ducts or lobules of the breast[17].

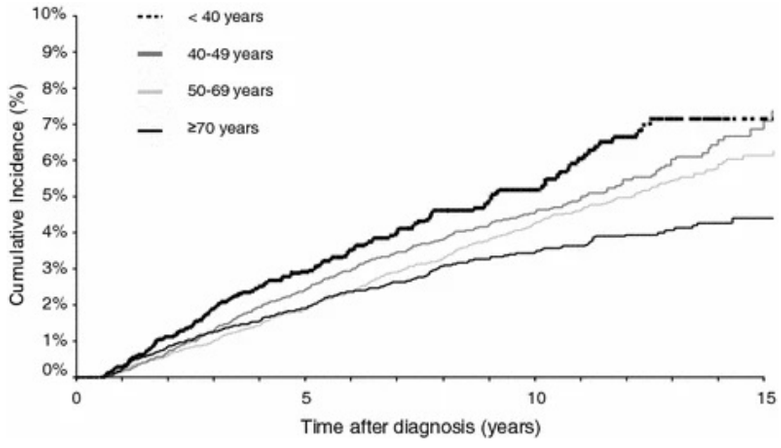


Figure 1: Cumulative incidence of contralateral breast cancer (CBC) by age and time since diagnosis (Data source: Netherlands Cancer Registry, N=45,229 index cancers; N=1,477 CBC[14], reproduced with permission of Breast Cancer Research and Treatment)

Contralateral breast cancer prevention: the preventive mastectomy

Although contralateral breast cancer risk is relatively low, an increasing number of patients with first breast cancer opt for a contralateral preventive mastectomy[18]. The rationale behind the contralateral preventive mastectomy is to avoid contralateral breast cancer with the consequent treatments and to potentially prevent death from a secondary primary breast cancer[19]. Among patients with highly elevated breast cancer risk contralateral preventive mastectomy is recommended, especially in patients with genetic predisposition or strong family history of breast cancer[20,21]. Currently, the contralateral preventive mastectomy is recommended in patients with germline mutations in *BRCA1* and *BRCA2* genes, although mutations in other breast cancer risk genes (*CHEK2, ATM* and *PALB2*) are suggested to also be associated with contralateral breast cancer risk[22-25].The 10-year contralateral breast cancer risk in women with *BRCA1*/2 germline mutations was estimated between 20-30% (Figure 2) [20-22,26]. Although the contralateral breast cancer risk is considerably high in women with *BRCA1/2* germline mutation, only between 1-5% of the European-descent general breast cancer population has a mutation in these genes[20,22,27]. Consequently, the choice of contralateral preventive mastectomy remains still debatable in a large part of general breast cancer population without any genetic predisposition. Furthermore, the increasing usage of (neo)adjuvant systemic therapies (chemo and endocrine therapy), intended to prevent breast cancer recurrences, has also been demonstrated to indirectly reduce the risk/incidence of contralateral breast cancer[12,18].

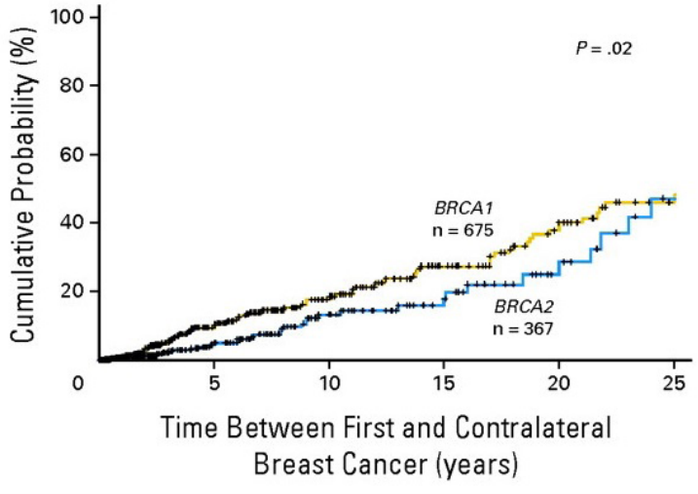


Figure 2: cumulative incidence of contralateral breast cancer in patients with *BRCA1/2* germline mutation (Data source: the German Consortium for Hereditary Breast and Ovarian Cancer, N=1,042; CBC=135[26], reproduced with permission from Journal of Clinical Oncology)

Decision-making for mastectomy

Psychological factors play a substantial role in a patient's decision regarding contralateral preventive mastectomy and in the outcome perceptions[18,28,29]. The risk reducing benefit of the surgery is commonly recognized. Contralateral preventive mastectomy mostly avoids a new breast cancer diagnosis and the subsequent new treatments[18,28]. As a consequence, contralateral preventive mastectomy might improve survival of first breast cancer patients. On the other hand, this intervention is not without negative consequences: approximately 30 out of 100 of women experience difficulties with body image, feminine identity, and sexual intimacy after surgery[18]. In addition, about 15-20% of patients who undergo contralateral preventive mastectomy may experience postoperative complications leading to higher medical costs and a potential lower quality of life[29-31]. Contralateral preventive mastectomy complications at (or about) the time of first breast cancer diagnosis may cause delays in initiating adjuvant systemic therapies increasing chance of breast cancer recurrences[29,30]. The benefit of avoiding the potential subsequent second breast cancer treatments should be correctly weighed against the costs of a negative body image and the potential postoperative complications. This harm and costs evaluation may be important during the consultation between patients and physicians to take a decision about the contralateral preventive mastectomy.

What is the role for prediction models in contralateral breast cancer prevention?

An appropriate risk prediction is crucial to more objectively quantify harms and benefit for a clinical decision making. Individualized contralateral risk prediction might help shared decision-making of physicians and patients about prevention strategies for those at high contralateral breast cancer risk, and to avoid unnecessary contralateral preventive mastectomies when contralateral breast cancer risk is low. Thus, contralateral breast cancer risk should be formally calculated to help patients and physicians during the decision making process towards preventive strategies, especially regarding contralateral preventive mastectomy[19]. This ambition may be successfully achieved under several conditions. First of all, the predicted risks should be sufficiently accurate and reliable. Good quality of data and performance assessment of the predicted risks is essential to evaluate prediction accuracy or to investigate the reasons causing inaccurate estimations. Secondly, the expected benefit of a clinical decision should be precisely quantified weighing pros and cons regarding preventive strategies. Last but not least, as long as predictions are accurate and the expected benefit is properly quantified, risk communication is really important in informing patients and physicians. Different methods of risk visualization may facilitate risk communication and the use of prediction tools in clinical practice[32].

Regression is the most widely statistical technique used to develop a risk prediction model and to provide absolute risk prediction[33]. A risk prediction model exploits the relation between predictors and the outcome of interest in a representative sample of patients. In

many cancer studies, the main outcome of interest is time until an event occurs, generally known as survival time. The methods considering survival time as outcome are defined as survival analysis [34]. However, when the event (e.g., death) does not occur in all individuals by the end of the follow-up, the true survival time is not known. This analytical problem is defined as censoring. Typically, censoring occurs when: a person does not experience the event of interest before the study ends, a person is lost to follow-up during the study, or a person withdraws from the study. The latter may happen when a competing event occurs. Let contralateral breast cancer event be the event of interest, patients may withdraw from the study because of dying. Therefore, death is a competing event that precludes the contralateral breast cancer from happening. Statistical models accounting for both censoring, and competing risks exist and are widely used in clinical practice such as in cardiology and oncology[35-37]. The most common statistical regression models for survival analysis with or without competing risks are the Cox proportional hazard regression and the Fine and Gray regression model[37].

Evaluation of performance and utility of risk prediction models

The statistical performance of a risk prediction model is important to validly support decision-making. A risk prediction model's performance is measured usually in terms of discrimination and calibration. The former is the ability of the model to identify subjects with good outcome and with poor outcome[38,39]. The latter is the agreement between observed and predicted outcome[38]. Both can be evaluated in the development data as internal validation or in independent data as external validation. The latter assessment provides an indication about the generalizability and the transportability of the risk prediction model in a new setting[40,41]. An increasing number of performance measures have been proposed in the last two decades for survival models. Many extend to the case of competing risks. However, clear guidance is lacking for a comprehensive assessment of the performance for survival and competing risks models [42-44]. Moreover, a model may show good performance in terms of discrimination and calibration, while both measures are unable to provide an answer to the question whether a risk prediction model should be used in practice to guide clinical decision making[45].

Net benefit is a relative novel measure to evaluate the clinical utility of risk prediction models and diagnostic tests weighting benefit and harms of a clinical decision making in public health[46,47]. Early detection and disease prevention are two of the most important goals in medicine. Physicians generally accept to recommend to persons or patients a certain number of unnecessary preventive strategies or treatments for the benefit to early detect or prevent a disease. This implies that the cost of missing the early detection or prevention of a certain disease (defined as false negatives) is typically more important than the cost of unnecessary preventive strategies or treatments recommendation (defined as false positives). The nationwide mammography screening program is a clear

example: public health physicians accept to recommend a high number of unnecessary screenings in a large population of healthy women to early detect a breast cancer with the aim to anticipate treatment and improve prognosis. This is also feasible because mammography screenings are considered as an acceptable safe procedure with a low number of side effects. In disease prevention, treatments or preventive strategies like surgeries may be more harmful than the mammography screening. For example, as previously mentioned, a certain number of complications after a contralateral preventive mastectomy may be possible.

Imagine having to decide about contralateral preventive mastectomy in 1000 patients diagnosed with first breast cancer. As previously reported, about 50 out of 1000 patients will develop a cancer in the contralateral breast in 10 years (i.e., as previously reported an expected 5% 10-year cumulative incidence). Suppose physicians recommend contralateral preventive mastectomy to all breast cancer patients irrespective of their age, potential germline mutations, family history and the other first breast cancer characteristics. We define this strategy as "intervention to all". This means we prevent 50 contralateral breast cancers (i.e., 5% benefit) at the cost of 950 unnecessary surgeries (i.e., 95% harm). Now, suppose that another strategy (named "alternative strategy", e.g., using a risk prediction model) is available and it reduces the number of unnecessary surgeries to 450, but preventing only 40 contralateral breast cancers. Is reducing 500 unnecessary surgeries at the cost of not preventing 10 contralateral breast cancers a good trade-off? To answer this question, it is important that physicians define how many patients should unnecessary undergo the contralateral preventive mastectomy to prevent one contralateral breast cancer. For example, a physician thinks that no more than 25 patients should undergo the surgery to prevent one contralateral breast cancer: this implies that not preventing a contralateral breast cancer is twenty-four times more harmful than undergoing an unnecessary preventive surgery. This 1:25 ratio would imply a decision threshold of 4%, and a relative weight of unnecessary surgery as 1/24 that of missing one contralateral breast cancer. The result of the net benefit calculation is reported in Table 1.

The net benefit is 1% and 2% for the strategy "interventions to all" and "alternative strategy", respectively. In other words, assuming the same number of unnecessary interventions, the "alternative strategy" prevents 20 contralateral breast cancers per 1000 patients at risk. The "intervention to all" strategy leads to prevent less contralateral breast cancers (i.e., 10) than the "alternative strategy". Thus, the net benefit of the "alternative strategy" is higher than the "intervention to all" strategy using 1/24 as weight of benefit and harms. However, physicians may have different opinions about how many patients should undergo unnecessary surgeries to prevent one disease. For this reason, net benefit calculation may be possible to define which strategy has higher net benefit using different exchange rates[46-48].

Table 1: an example of net benefit calculation

How many unnecessary mastectomies a physician is willing to accept to prevent a contralateral breast cancer?	Number of patients with first breast cancer: 1000 Expected number of contralateral breast cancers in 10 years: 50				
	Exchange rate	Strategies	Benefit	Harm	Net Benefit = benefit - (harm × exchange rate)
25	1/24	Interventions to all	5% (50/1000)	95% (950/1000)	5% - (95% ×1/24) = 1%
		Alternative strategy	4% (40/1000)	45% (450/1000)	4% - (45% ×1/24) = 2%

The goal of this thesis is to develop, validate and evaluate the potential clinical utility of a contralateral breast cancer prediction model to provide contralateral breast cancer prediction at 5 and 10 years since diagnosis of first primary breast cancer. Frameworks of assessing prediction performance in time-to-event models with or without competing risks are proposed using motivating examples in breast cancer.

THESIS OUTLINE

We set out to develop a risk prediction model for contralateral breast cancer. named PredictCBC, using international population-based and hospital-based studies (Table 2, Chapter 2).

Table 2: Data sources used in the thesis

Source	Country	Description	Chapter
Amsterdam Breast Cancer Study (ABCS)	the Netherlands	Hospital-based study	2-3-4
Breast Cancer Association Consortium (BCAC)	International	Population and hospital-based studies	2-3-4
Breast Cancer Outcome Study of Mutation (BOSOM)	the Netherlands	Hospital-based study	2-3-4
Erasmus Medical Center (EMC)	the Netherlands	Hospital-based study	2-3-4
Hereditary Breast and Ovarian cancer study (HEBON)	the Netherlands	Population-based study*	4
the Netherlands Cancer Registry (NCR)	the Netherlands	Population-based study	2-3-4-5-7

*selection through clinical genetic centers

Using the same data (Table 2), we evaluated and compared the prediction performance of PredictCBC with other tools available to calculate the contralateral breast cancer risk in clinical practice: CBCrisk and the Manchester formula (Chapter 3). We updated PredictCBC models using more clinical and genetic information available including body mass index, parity, *CHEK2* c.1100del, and polygenic risk score to potentially improve the contralateral breast cancer risk prediction performance for decision making (Chapter 4). We estimated the contralateral breast cancer risk in patients with ductal carcinoma in situ, a possible precursor of breast cancer since less is known about contralateral breast cancer risk in comparison with invasive breast cancer patients (Chapter 5). Finally, we provide frameworks of how to assess prediction performance in time-to-event models with and without competing risks using motivating examples in breast cancer as a guidance for researchers and practitioners interested in risk prediction (Chapter 6 and Chapter 7).

REFERENCES

1 Bray, F. *et al.* Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* **68**, 394-424, doi:10.3322/caac.21492 (2018).

2 Netherlands Cancer Registry (NCR). *Survival and prevalence of cancer*, <https://www.cijfersoverkanker.nl> (2016).

3 van der Meer, D. J. *et al.* Comprehensive trends in incidence, treatment, survival and mortality of first primary invasive breast cancer stratified by age, stage and receptor subtype in the Netherlands between 1989 and 2017. *Int J Cancer* **148**, 2289-2303, doi:10.1002/ijc.33417 (2021).

4 Brenner, D. J. Contralateral second breast cancers: prediction and prevention. *J Natl Cancer Inst* **102**, 444-445, doi:10.1093/jnci/djq058 (2010).

5 Mariani, L. *et al.* Prognostic factors for metachronous contralateral breast cancer: a comparison of the linear Cox regression model and its artificial neural network extension. *Breast Cancer Res Treat* **44**, 167-178, doi:10.1023/a:1005765403093 (1997).

6 Veronesi, U. *et al.* Twenty-year follow-up of a randomized study comparing breast-conserving surgery with radical mastectomy for early breast cancer. *N Engl J Med* **347**, 1227-1232, doi:10.1056/NEJMoa020989 (2002).

7 Schaapveld, M. *et al.* Risk of new primary nonbreast cancers after breast cancer treatment: a Dutch population-based study. *J Clin Oncol* **26**, 1239-1246, doi:10.1200/JCO.2007.11.9081 (2008).

8 Cheung, K. J. & Davidson, N. E. Double Trouble: Contralateral Breast Cancer Risk Management in the Modern Era. *J Natl Cancer Inst* **111**, 641-643, doi:10.1093/jnci/djy203 (2019).

9 Curtis, R. E., Ron, E., Hankey, B. F. & Hoover, R. N. in *New malignancies among cancer survivors: SEER Cancer Registries, 1973–2000* (ed National Institutes of Health (NIH)) pp 185-2005 (2006).

10 Soerjomataram, I. *et al.* Risks of second primary breast and urogenital cancer following female breast cancer in the south of The Netherlands, 1972-2001. *Eur J Cancer* **41**, 2331-2337, doi:10.1016/j.ejca.2005.01.029 (2005).

11 Chen, Y., Thompson, W., Semenciw, R. & Mao, Y. Epidemiology of contralateral breast cancer. *Cancer Epidemiol Biomarkers Prev* **8**, 855-861 (1999).

12 Kramer, I. *et al.* The influence of adjuvant systemic regimens on contralateral breast cancer risk and receptor subtype. *J Natl Cancer Inst*, doi:10.1093/jnci/djz010 (2019).

13 Vichapat, V. *et al.* Prognosis of metachronous contralateral breast cancer: importance of stage, age and interval time between the two diagnoses. *Breast Cancer Res Treat* **130**, 609-618, doi:10.1007/s10549-011-1618-8 (2011).

14 Schaapveld, M. *et al.* The impact of adjuvant therapy on contralateral breast cancer risk and the prognostic significance of contralateral breast cancer: a population based study in the Netherlands. *Breast Cancer Res Treat* **110**, 189-197, doi:10.1007/s10549-007-9709-2 (2008).

15 Langballe, R. *et al.* Mortality after contralateral breast cancer in Denmark. *Breast Cancer Res Treat* **171**, 489-499, doi:10.1007/s10549-018-4846-3 (2018).

16 Hartman, M. *et al.* Incidence and prognosis of synchronous and metachronous bilateral breast cancer. *J Clin*

Oncol **25**, 4210-4216, doi:10.1200/JCO.2006.10.5056 (2007).

17 Mariotti, C. Ductal Carcinoma in Situ of the Breast. *Springer International Publishing* (2018).

18 Murphy, J. A., Milner, T. D. & O'Donoghue, J. M. Contralateral risk-reducing mastectomy in sporadic breast cancer. *Lancet Oncol* **14**, e262-269, doi:10.1016/S1470-2045(13)70047-0 (2013).

19 Narod, S. A. Bilateral breast cancers. *Nat Rev Clin Oncol* **11**, 157-166, doi:10.1038/nrclinonc.2014.3 (2014).

20 van den Broek, A. J. *et al.* Impact of Age at Primary Breast Cancer on Contralateral Breast Cancer Risk in BRCA1/2 Mutation Carriers. *J Clin Oncol* **34**, 409-418, doi:10.1200/JCO.2015.62.3942 (2016).

21 Kuchenbaecker, K. B. *et al.* Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA* **317**, 2402-2416, doi:10.1001/jama.2017.7112 (2017).

22 Weischer, M. *et al.* CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. *J Clin Oncol* **30**, 4308-4316, doi:10.1200/JCO.2012.42.7336 (2012).

23 Broeks, A. *et al.* Excess risk for contralateral breast cancer in CHEK2*1100delC germline mutation carriers. *Breast Cancer Res Treat* **83**, 91-93, doi:10.1023/B:BREA.0000010697.49896.03 (2004).

24 Robson, M. E. *et al.* Association of Common Genetic Variants With Contralateral Breast Cancer Risk in the WECARE Study. *J Natl Cancer Inst* **109**, doi:10.1093/jnci/djx051 (2017).

25 Fanale, D. *et al.* Detection of Germline Mutations in a Cohort of 139 Patients with Bilateral Breast Cancer by Multi-Gene Panel Testing: Impact of Pathogenic Variants in Other Genes beyond BRCA1/2. *Cancers (Basel)* **12**, doi:10.3390/cancers12092415 (2020).

26 Graeser, M. K. *et al.* Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. *J Clin Oncol* **27**, 5887-5892, doi:10.1200/JCO.2008.19.9430 (2009).

27 Thompson, D. & Easton, D. The genetic epidemiology of breast cancer genes. *J Mammary Gland Biol Neoplasia* **9**, 221-236, doi:10.1023/B:JOMG.0000048770.90334.3b (2004).

28 Ager, B. *et al.* Contralateral prophylactic mastectomy (CPM): A systematic review of patient reported factors and psychological predictors influencing choice and satisfaction. *Breast* **28**, 107-120, doi:10.1016/j.breast.2016.04.005 (2016).

29 Agarwal, S., Pappas, L., Matsen, C. B. & Agarwal, J. P. Second primary breast cancer after unilateral mastectomy alone or with contralateral prophylactic mastectomy. *Cancer Med*, doi:10.1002/cam4.3394 (2020).

30 Keskey, R. C. *et al.* Cost-effectiveness Analysis of Contralateral Prophylactic Mastectomy Compared to Unilateral Mastectomy with Routine Surveillance for Unilateral, Sporadic Breast Cancer. *Ann Surg Oncol* **24**, 3903-3910, doi:10.1245/s10434-017-6094-x (2017).

31 Parker, P. A. *et al.* Prospective Study of Psychosocial Outcomes of Having Contralateral Prophylactic Mastectomy Among Women With Nonhereditary Breast Cancer. *J Clin Oncol* **36**, 2630-2638, doi:10.1200/JCO.2018.78.6442 (2018).

32 Van Belle, V. & Van Calster, B. Visualizing Risk Prediction Models. *PLoS One* **10**, e0132614, doi:10.1371/journal.pone.0132614 (2015).

33 Harrell, F. E., Jr. Regression Modeling Strategies with applications to linear models, logistic and ordinal regression, and survival analysis. *Springer Series in Statistics* **2nd edition** (2015).

34 Clark, T. G., Bradburn, M. J., Love, S. B. & Altman, D. G. Survival analysis part I: basic concepts and first analyses. *Br J Cancer* **89**, 232-238, doi:10.1038/sj.bjc.6601118 (2003).

35 Haller, B., Schmidt, G. & Ulm, K. Applying competing risks regression models: an overview. *Lifetime Data Anal* **19**, 33-58, doi:10.1007/s10985-012-9230-8 (2013).

36 Austin, P. C., Lee, D. S. & Fine, J. P. Introduction to the Analysis of Survival Data in the Presence of Competing Risks. *Circulation* **133**, 601-609, doi:10.1161/CIRCULATIONAHA.115.017719 (2016).

37 Wolbers, M., Koller, M. T., Witteman, J. C. & Steyerberg, E. W. Prognostic models with competing risks: methods and application to coronary risk prediction. *Epidemiology* **20**, 555-561, doi:10.1097/EDE.0b013e3181a39056 (2009).

38 Steyerberg, E. W. *et al.* Assessing the performance of prediction models: a framework for traditional and novel measures. *Epidemiology* **21**, 128-138, doi:10.1097/EDE.0b013e3181c30fb2 (2010).

39 Pencina, M. J. & D'Agostino, R. B., Sr. Evaluating Discrimination of Risk Prediction Models: The C Statistic. *JAMA* **314**, 1063-1064, doi:10.1001/jama.2015.11082 (2015).

40 Steyerberg, E. W. & Harrell, F. E., Jr. Prediction models need appropriate internal, internal-external, and external validation. *J Clin Epidemiol* **69**, 245-247, doi:10.1016/j.jclinepi.2015.04.005 (2016).

41 Austin, P. C. *et al.* Geographic and temporal validity of prediction models: different approaches were useful to examine model performance. *J Clin Epidemiol* **79**, 76-85, doi:10.1016/j.jclinepi.2016.05.007 (2016).

42 van Houwelingen, H. C. Validation, calibration, revision and combination of prognostic survival models. *Stat Med* **19**, 3401-3415 (2000).

43 Kamarudin, A. N., Cox, T. & Kolamunnage-Dona, R. Time-dependent ROC curve analysis in medical research: current methods and applications. *BMC Med Res Methodol* **17**, 53, doi:10.1186/s12874-017-0332-6 (2017).

44 Austin, P. C., Harrell, F. E., Jr. & van Klaveren, D. Graphical calibration curves and the integrated calibration index (ICI) for survival models. *Stat Med* **39**, 2714-2742, doi:10.1002/sim.8570 (2020).

45 Vickers, A. J., Van Calster, B. & Steyerberg, E. W. Net benefit approaches to the evaluation of prediction models, molecular markers, and diagnostic tests. *BMJ* **352**, i6, doi:10.1136/bmj.i6 (2016).

46 Vickers, A. J. & Elkin, E. B. Decision curve analysis: a novel method for evaluating prediction models. *Med Decis Making* **26**, 565-574, doi:10.1177/0272989X06295361 (2006).

47 Vickers, A. J., Cronin, A. M., Elkin, E. B. & Gonen, M. Extensions to decision curve analysis, a novel method for evaluating diagnostic tests, prediction models and molecular markers. *BMC Med Inform Decis Mak* **8**, 53, doi:10.1186/1472-6947-8-53 (2008).

48 Kerr, K. F., Brown, M. D., Zhu, K. & Janes, H. Assessing the Clinical Impact of Risk Prediction Models With Decision Curves: Guidance for Correct Interpretation and Appropriate Use. *J Clin Oncol* **34**, 2534-2540, doi:10.1200/JCO.2015.65.5654 (2016).