Prediction of contralateral breast cancer: statistical aspects and prediction performance

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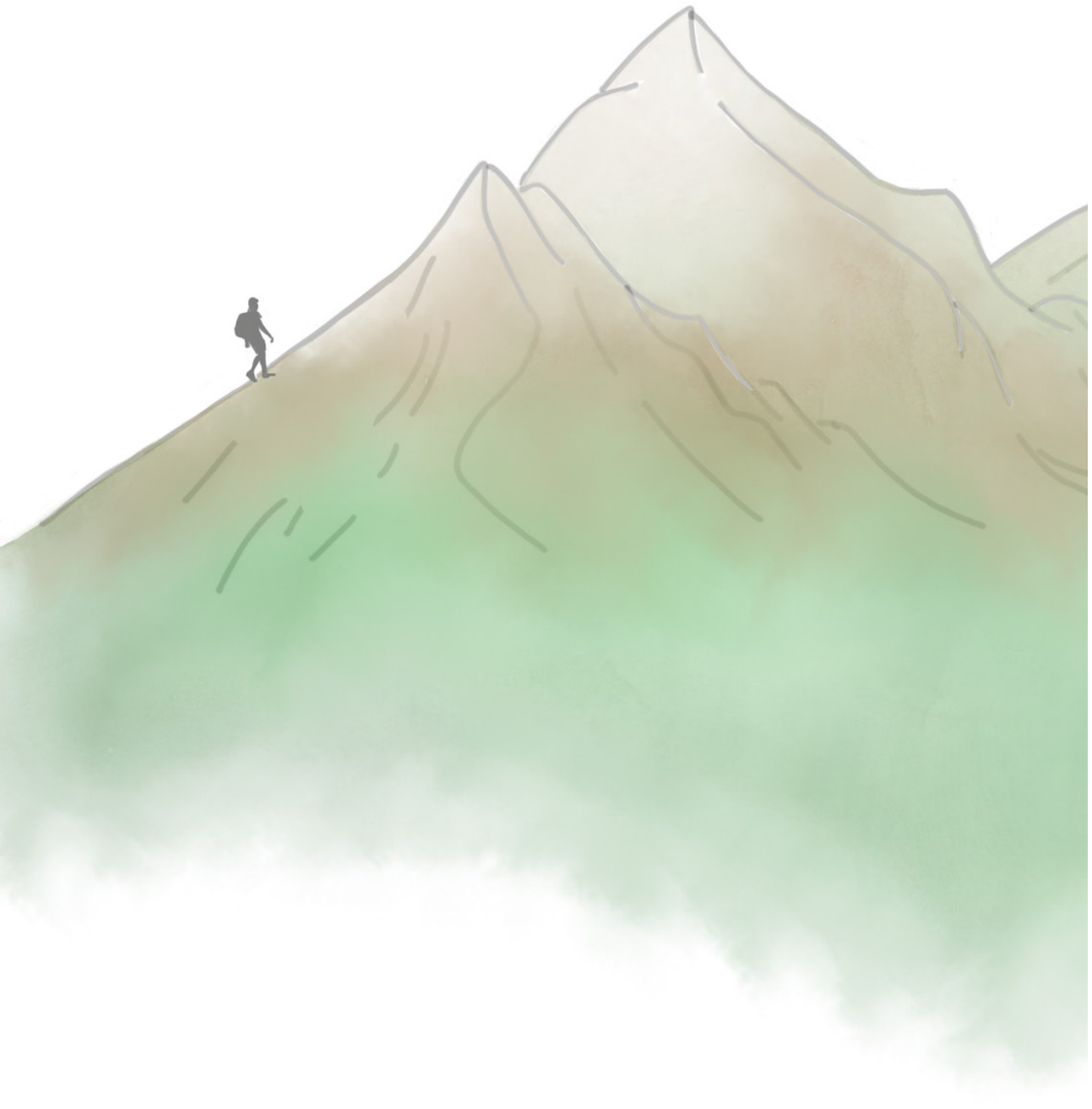

Chapter 9

Summary

SUMMARY OF MAIN FINDINGS

Prediction of contralateral breast cancer

Breast cancer is the most common cancer among women worldwide. Although the incidence of breast cancer has increased, 10-year survival has improved approximately from 40% in 1960 and 1970 to almost 80% in 2010, in Europe. This rise may be attributed to early detection and better treatment modalities. The increase in diagnosis of first primary breast cancer implies that there are also more women at risk to develop a second primary tumor in the opposite breast. This is because contralateral breast cancer is the most common second primary cancer among women diagnosed with first breast cancer and accounts for approximately 40-50% of all new second cancers. On average, four to five out of 100 women with primary breast cancer develop a contralateral breast cancer within 10 years. These women have a worse prognosis compared with patients with unilateral breast cancer. Women with first primary breast cancer and high risk of contralateral breast cancer may opt for a contralateral preventive mastectomy, to almost nullify the risk to develop a contralateral breast cancer. In women at elevated contralateral breast cancer risk, such as women with pathogenic mutations in the *BRCA1*, *BRCA2*, or in the *CHEK2* genes or with a family history of (bilateral) breast cancer, the option of contralateral preventive mastectomy is actively discussed by clinicians. However, although contralateral preventive mastectomy is debatable in a large part of the breast cancer population without any genetic predisposition, an increasing number of women at low risk to develop a contralateral breast cancer choose to undergo a contralateral preventive mastectomy. Individualized contralateral breast cancer risk prediction may be potentially useful to facilitate shared decision making of physicians and patients regarding preventive strategies for those at high contralateral breast cancer risk and to avoid potentially unnecessary contralateral preventive mastectomies among patients at low risk to develop a contralateral breast cancer. One aim of this thesis was to develop and validate a contralateral breast cancer risk prediction model and evaluate its potential clinical utility (**chapter 1**).

In **chapter 2,** we developed and validated a contralateral breast cancer risk prediction model (PredictCBC). For this study, we used a large dataset of population- and hospital-based studies, mostly performed in Europe, United States and Australia, including more than 100,000 patients diagnosed with first invasive primary breast cancer between 1990-2013. PredictCBC provided the estimated 5- and 10-year risk to develop contralateral breast cancer using information about first primary breast cancer, family history, and *BRCA1/2* germline mutation status. We showed that the prediction performance accuracy of PredictCBC was moderate. PredictCBC may potentially tailor clinical decision making regarding preventive strategies that are currently essentially based on *BRCA1/2* germline mutation status. Contralateral preventive mastectomies might be unnecessary even in some patients with *BRCA1/2* germline mutations, especially among those with other favorable characteristics. On the other hand, preventive strategies such as personalized mammography screening might be necessary for non-*BRCA1/2* carrier patients, especially among those with unfavorable characteristics.

In **chapter 3,** we compared the prediction performance of PredictCBC with two other tools currently available to predict contralateral breast cancer: the Manchester formula and CBCrisk. The Manchester formula is a heuristic formula that estimates the lifetime contralateral breast cancer risk using information based on a systematic review of the literature. CBCrisk was developed using data on 1,921 contralateral breast cancer cases and 5,763 matched controls with first primary breast cancer. CBCrisk was externally validated in two independent studies in the United States. We externally validated the Manchester formula, and the contralateral breast cancer risk tools in the twenty studies used to develop and validate PredictCBC. We estimated that all three tools provided moderate individualized contralateral breast cancer prediction accuracy. For individual patients, we found a considerable heterogeneity of the prediction performances among the three tools. These differences reflect the heterogeneity among patients' characteristics and the corresponding contralateral breast cancer incidences among countries. We concluded that deeper biological and clinical insights, and the potential inclusion of genetic information beyond *BRCA1/2* germline mutation, might improve contralateral breast cancer prediction. In addition, this could further tailor clinical decision making about strategies for prevention or early detection of contralateral breast cancer. We encourage a more direct comparison between the three tools using large external datasets with complete information on all factors considered for contralateral breast cancer prediction models.

In **chapter 4**, we extended PredictCBC models by adding additional genetic information (e.g.: presence of the *CHEK2 c.11100delC* variant and a polygenic risk score based on 313 common genetic variants), and lifestyle and reproductive factors suggested to be associated with contralateral breast cancer. We developed and validated PredictCBC-2.0 models using updated follow-up information. We also extended the study population used to develop PredictCBC models including over 200,000 first primary breast cancer patients from a wide range of European-descendent studies diagnosed from 1990 to 2017. Additional genetic information beyond *BRCA1/2* germline mutation status improved contralateral breast cancer risk prediction. PredictCBC-2.0 might therefore help tailor clinical decision making towards contralateral preventive mastectomy or alternative preventive strategies such as personalized screening or personalized treatments.

In **chapter 5** we compared the contralateral breast cancer risk among patients diagnosed with first primary invasive breast cancer and patients diagnosed with ductal carcinoma

in situ, a potential precursor of cancer. We showed that the contralateral breast cancer risk is slightly higher in patients with ductal carcinoma in situ compared to invasive breast cancer patients using the Dutch cancer registry, a large population-based study in the Netherlands. Around five out of 100 patients with ductal carcinoma in situ may develop a contralateral breast cancer compared to around four patients among invasive breast cancer patients within 10 years. We concluded that this slightly higher contralateral breast cancer risk in ductal carcinoma in situ patients might be largely explained by that adjuvant systemic therapies in ductal carcinoma are not currently prescribed for ductal carcinoma in situ patients according to the current Dutch guidelines. This does not imply that we should start treating ductal carcinoma in situ patients with adjuvant systemic therapy since these patients have excellent prognosis and systemic therapy might have severe side effects. However, contralateral breast cancer prediction models may be useful for women with ductal carcinoma in situ as well to consider, for example, less or more intensified screening.

Assessing prediction performance with survival outcomes: practical guidance

Prediction research focuses on the development of well performing prediction models and on the assessment of their generalizability and applicability in clinical practice. A risk prediction model may be developed using regression, a statistical technique that estimates the relation between predictors and the outcome of interest (**chapter 1**). In many (breast) cancer studies, the outcome of interest is the time till an event occurs. Survival analysis is one of the most popular types of time-to-event analysis when the outcome is the survival time. When we study the occurrence of an event (e.g.: contralateral breast cancer) in a group of people, a person might not experience the event of interest over a certain time. In this case, survival time is censored. It might also happen that another event, different than the endpoint of interest, may preclude the event of interest from happening. For example, if we are studying contralateral breast cancer in women diagnosed with first primary breast cancer, some of them may die and those women will never be diagnosed with contralateral breast cancer since another competing (in this case fatal) event (or risk) occurred in their lives. 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, respectively. These statistical regression models may be used to predict that an event of interest (e.g.: contralateral breast cancer) may occur in a certain time in the future (e.g.: within 10 years). Once a risk prediction model has been developed, it is first important to assess its performance. At the first instance, it is common to assess the prediction performance of a risk prediction in the same underlying population used to develop the model. This process is defined as internal validation. External validation refers to the evaluation of the prediction performance in a plausibly related population, which requires an independent dataset which may differ in setting, time, or place. If the prediction performance is sufficiently accurate, the risk prediction model might be applied in clinical practice to facilitate decision making (e.g.: by patient and physician considering contralateral preventive mastectomy). A further aim of this thesis was to provide guidance for assessing the prediction performance of time-to-event models with or without competing risks using motivating examples in breast cancer (**chapter 1**).

In **chapter 6**, we provided guidance and recommendations for assessing prediction performance of survival models. We described different measures that may be used to assess the performance of a prediction model with a survival outcome. We made a distinction between measures that can be used to assess the performance of predictions for specific time points (e.g., 5- or 10-year survival) and over a range of follow-up time. Prediction at specific time points will often be most relevant since clinicians and patients are usually interested in prognosis within a specified time. We illustrated how to develop a risk prediction model with survival outcome, how to assess its prediction performance and clinical utility through internal and external validation using real breast cancer datasets with the accompanying R and SAS software code.

In **chapter 7**, we provided an accessible overview of performance measures for a comprehensive assessment of the performance of a competing risks prediction model. We focused on how to validate a risk prediction model in the presence of competing risks at a given prediction horizon, a specified duration of time over which predictions are made (e.g., at 5 years). We extensively illustrated different methods on how to develop a risk prediction model with competing risks and how to calculate and interpret its prediction performance and clinical utility with illustration using a prediction model for breast cancer recurrence, including accompanying R code. Both overviews in **Chapter 6 and 7** were made on behalf of the international STRengthening Analytical Thinking for Observational Studies (STRATOS) initiative (http://stratos-initiative.org), which aims to provide accessible and accurate guidance documents for relevant topics in the design and analysis of observational studies for a non-specialist audience.

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