ANALYSIS PLAN

Project: Prognosis, prognostic factors and predictive factors in centimeter or sub centimeter node-negative breast cancer

Date: 171110

Hypothesis:
- Established prognostic and/or predictive factors in overall breast cancer are prognostic and/or predictive factors also in centimeter or sub centimeter node-negative breast cancer.
- The established relative reduction in risk of recurrence and death of adjuvant treatment for overall breast cancer are similar in centimeter or sub centimeter node-negative breast cancer.

Specific aims:
1. To estimate prognosis among patients with T1abN0 tumors who have not received adjuvant treatment.
2. To estimate the effect of radiotherapy versus no radiotherapy on prognosis among patients with T1abN0 tumors.
3. To estimate the effect of endocrine therapy versus no endocrine therapy on prognosis among patients with estrogen receptor (ER) positive T1abN0 tumors.
4. To estimate the effect of chemotherapy versus no chemotherapy on prognosis among patients with T1abN0 tumors.
5. To estimate the effect of trastuzumab versus no trastuzumab on prognosis among patients with human epidermal growth factor receptor 2 (HER2) positive T1abN0 tumors.

We will explore if the prognosis and treatment effects differ by age at diagnosis, menopausal status, whether the tumor was screening detected or not, type of surgery performed, tumor size (within T1abN0 tumors), tumor grade, ER-status, HER2-status or the intrinsic subgroups of cancer. For comparison, we will run the abovementioned analyses among patients with node-positive T1ab tumors (i.e., T1abN1).

Start of follow-up:
January 1, 1977.

End of follow-up:
December 31, 2014 for breast cancer specific death.
July 30, 2016 for all-cause mortality.

Primary endpoints:
1. Death from breast cancer.

Secondary endpoints:
1. Death from any cause.
2. Ipsilateral or contralateral breast cancer (i.e., metachronous breast cancer).

Inclusion criteria:
2. Tumor size ≤10 mm.
3. Female sex.

Exclusion criteria:
1. Metastatic disease at diagnosis (i.e., M1).
2. Prior breast cancer.
**Statistical analyses:**
The cohort members will be followed from the date of breast cancer diagnosis to the date of breast cancer death (i.e., the primary outcome), emigration, death from other causes than breast cancer, or end of follow-up, whichever occurs first. As a sensitivity analysis, women with metachronous breast cancer will be censored at the time of diagnosis of the metachronous tumor. As a sensitivity analysis, women with any prior cancer, except non-melanoma skin cancer and cancer in situ of the cervix, will be excluded.

Survival rates will be estimated using the Kaplan-Meier method and statistical comparisons between relevant exposure groups will be conducted using the log-rank test. Cox proportional hazard regression will be used to calculate multivariable hazard ratios (HRs) and 95% confidence intervals (CI) of the association between relevant exposure groups and outcome.

For each cohort member (i.e., index case), 10 comparators have been randomly selected from the general population based on the following criteria: 1) alive at the date of diagnosis of breast cancer for the index case; 2) not diagnosed with breast cancer at the date of diagnosis of breast cancer for the index case; 3) same age as the index case; 4) residing in the same County Council as the index case at the date of diagnosis of breast cancer for the index case. We will calculate relative survival rates in 5-year intervals (at 5, 10, 15 years etc.).

**Exposure groups:**
1. No adjuvant treatment.
2. Radiotherapy versus no radiotherapy.
3. Endocrine treatment versus no endocrine therapy (in women with hormone receptor positive\(^1\) disease).
4. Chemotherapy versus no chemotherapy.
5. Trastuzumab versus no trastuzumab (in women with HER2-positive disease).

**Subgroups:**
1. Tumor size (\(\leq 5\) mm, 6-\(\leq 10\) mm).
2. N-status (N0, N1, missing).
3. Age at diagnosis (<35, 35-\(<50\), 50-\(<70\), \(\geq 70\)).
5. Screening detected tumor (yes, no, missing).
6. Type of surgery (partial mastectomy, mastectomy, other/missing).
7. Tumor grade (1, 2, 3, missing).
8. ER-status (positive, negative, missing).
9. HER2-status (positive, negative, missing).
10. Intrinsic subgroup proxy (Luminal A\(^2\), Luminal B (HER2-negative)\(^3\), Luminal B (HER2-positive)\(^4\), HER2-positive (non-luminal)\(^5\), Triple negative\(^6\), missing).
11. Radiotherapy (yes, no, missing).
12. Endocrine treatment (yes, no, missing).
13. Chemotherapy (yes, no, missing).
14. Trastuzumab (yes, no, missing).

**Notes:**
1) Hormone receptor positive disease = ER-positive and/or PR-positive.
2) Luminal A = ER-positive, PR-positive, HER2-negative and Grade 1-2.
3) Luminal B (HER2-negative) = ER-positive, HER2-negative and PR-negative and/or Grade 3.
4) Luminal B (HER2-positive) = ER-positive and HER2-positive.
5) HER2-positive (non-luminal) = ER-negative, PR-negative and HER2-positive.
6) Triple negative = ER-negative, PR-negative and HER2-negative.