Supplementary Material to: Regularized Bidimensional Estimation of the Hazard Rate

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1 Application to Breast Cancer Mortality: Stratification with respect to the Age at Diagnosis

The mortality of breast cancer is known to greatly vary on whether the cancer is pre or post-menopausal (Consensus, 1985). Consequently, a thorough analysis of the mortality from breast cancer would require to stratify with respect to the menopausal status at diagnosis. Since this covariate is not present in the data, we decided to stratify the sample with respect to the age of the patient at diagnosis, which is a proxy of menopausal status. Most women are known to have their menopause between 45 and 55 years old (Hill, 1996; Henderson et al., 2008; Gold, 2011), with 25th, 50th, 75th percentiles ranging from years 47-49, 50-51, 52-54, respectively, according to countries and surveys (Mishra et al., 2017). Consequently, based on the available information in SEER, for each cancer stage, the patients were divided into three classes of age at diagnosis: $(.,45]$, $(45,55]$, and $(55,.)$ as a proxy for pre- menopausal, peri- menopausal and post- menopausal ages, respectively. The resulting estimated hazards are represented in Figure 1.

The stage 1 cancer patients younger than 45 and the stage 3 cancer patients older than 55 display the same mortality across all dates of diagnosis, i.e. with no cohort effect.

Moreover, the mortality of stage 1 cancer patients aged 45 and older at diagnosis has a slight cohort effect corresponding to a progressive decrease in the mortality across all survival times (Peto et al., 2000). This could suggest a trend of slow and steady improvement of the treatment of breast cancer in the United States over the period $1887-2005$.

Finally, we observe a clear decrease of the mortality for stage 2 cancers for all three age classes. This shift is located at the year 1995 for middle-aged patients and around the years $1997-1998$ for patients younger than 45 and older than 55. The same drop in mortality is observed for stage 3 cancers with patients younger than 45 at diagnosis, around year 1995. This could correspond to the introduction of improvements in the treatments of breast cancer in the United States (Consensus, 1985). Among the three main medical innovations, which can be considered in this period, the improvement of the surgical procedures for the loco- regional control of the disease and the assessment

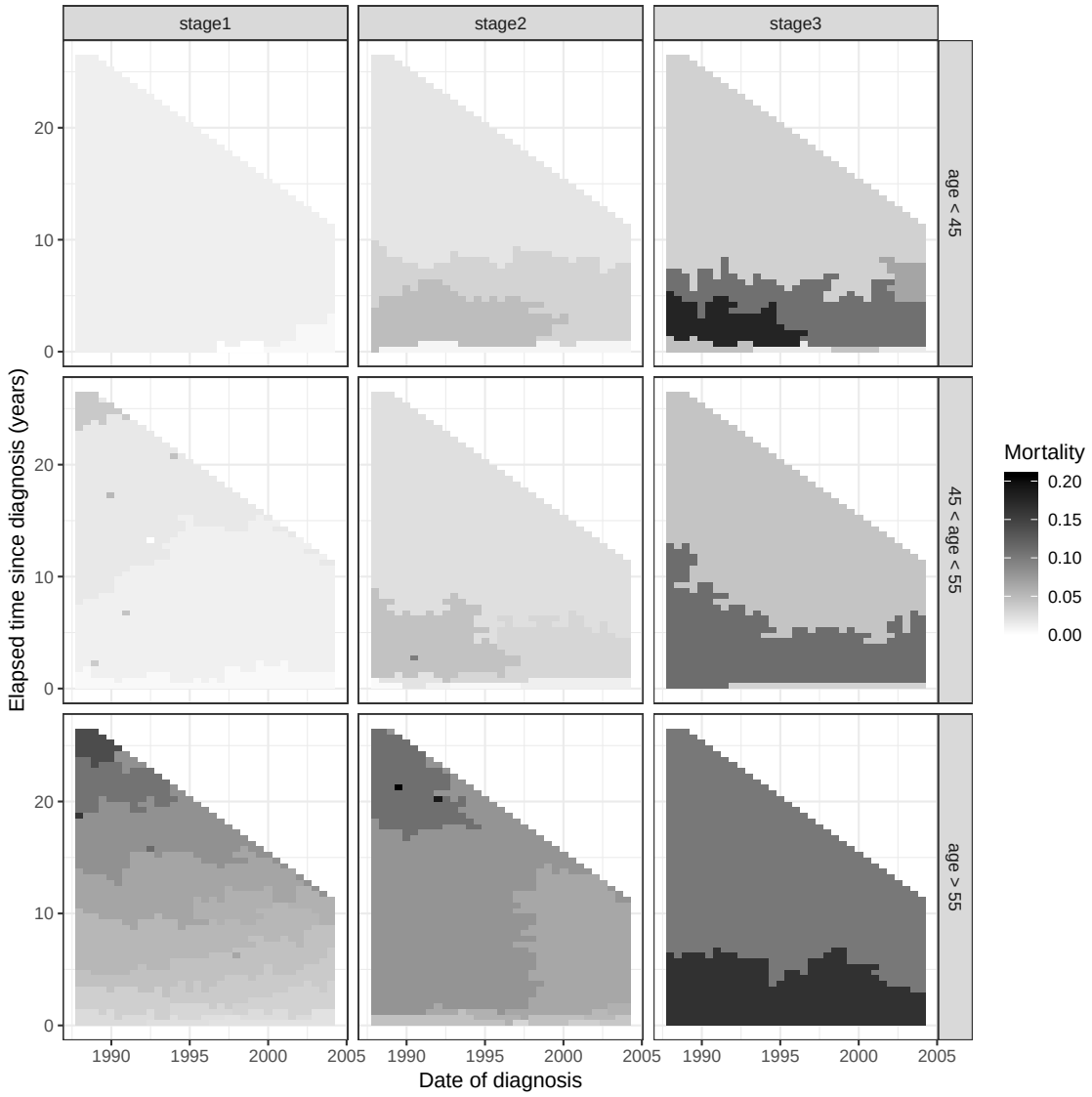

Figure 1: Estimated hazard of death since diagnosis of breast cancer for different cancer stages and for different ages at diagnosis. The estimate is obtained with the L_0 regularization. The upper right corner of every graph corresponds to the region where no data are available. All graphs share the same scale.

of the beneficial effect of hormone-receptor therapies could be reflected in the observed survival in stages 1-2, whereas the later emergence during this period of new classs of chemotherapeutic agents like taxoids (Rowinsky et al., 1992; Crown et al., 2004) or herceptin-based therapies targeted on new class of tumor markers (Pegram et al., 1998; Emens and Davidson, 2004) would be related with the changes in survival observed in stage 3. In the next section, we will use a stratified analysis to understand the effect of hormone-receptor therapies on the mortality shift in the mid-1990s.

2 Application to Breast Cancer Mortality: Stratification with respect to the Estrogen Receptor Status

The cohort effect highlighted in the previous section could correspond to the introduction of Selective Estrogen Receptor Modulator (SERM) treatments and in particular the use of Tamoxifen as a treatment for breast cancer, showing improved survival in women with estrogen receptor positive tumor, initially in post- menopausal women (Fisher et al., 1989), later in both post - and premenopausal women (Early Breast Cancer Trialists' Collaborative Group, 1988; Fisher et al., 1998; Pritchard, 2005; Cochrane, 2008). Indeed, Tamoxifen was gradually used in the early years of 1990's (Gail et al., 1999; Harlan et al., 2002; Mariotto et al., 2006) to decrease the mortality of breast cancer patients. This treatment is only efficient on estrogen receptor-sensitive cancers. To validate our hypothesis, we conducted the estimation of mortality separately for patients with estrogen receptor sensitive and non-sensitive cancers. Since stage 2 cancers displayed a strong cohort effect across all ages at diagnosis, we only kept stage 2 cancers in this study. The estimated mortality is given in Figure 2. Note that the spikes in the mortality are an artifact of the segmentation procedure when the sample sizes tend to be too small in some regions of the age-cohort plane and are not to be taken into account in the interpretation of the mortality.

There is a clear difference in the evolution of mortality with respect to time at diagnosis between sensitive and non-sensitive estrogen cancers. For estrogen sensitive cases, the mortality displays the same sudden decrease around years $1997 - 1998$ as in Figure 1, across all age classes. In particular for individuals aged 55 or more at the time of diagnosis, the mortality has gradually decreased for estrogen sensitive patients, whereas it did not evolve with time for estrogen non-sensitive patients. On the other hand, the mortality for non-estrogen sensitive cancers displays almost no cohort effect for all ages at diagnosis (Knight et al., 1977).

The same analysis was run with stratification with respect to progesterone receptor status, with very similar morality estimates (results not shown here). Further analyses could be carried out to better understand the effect of the introduction of hormone-blocking therapies on mortality. However, the segmentation of the hazard rate, even with this simple stratified analysis, highlighted that the adoption of SERM therapies in the United States is a potential reason for the sharp decrease of mortality in the middle of the 1990s (Peto et al., 2000).

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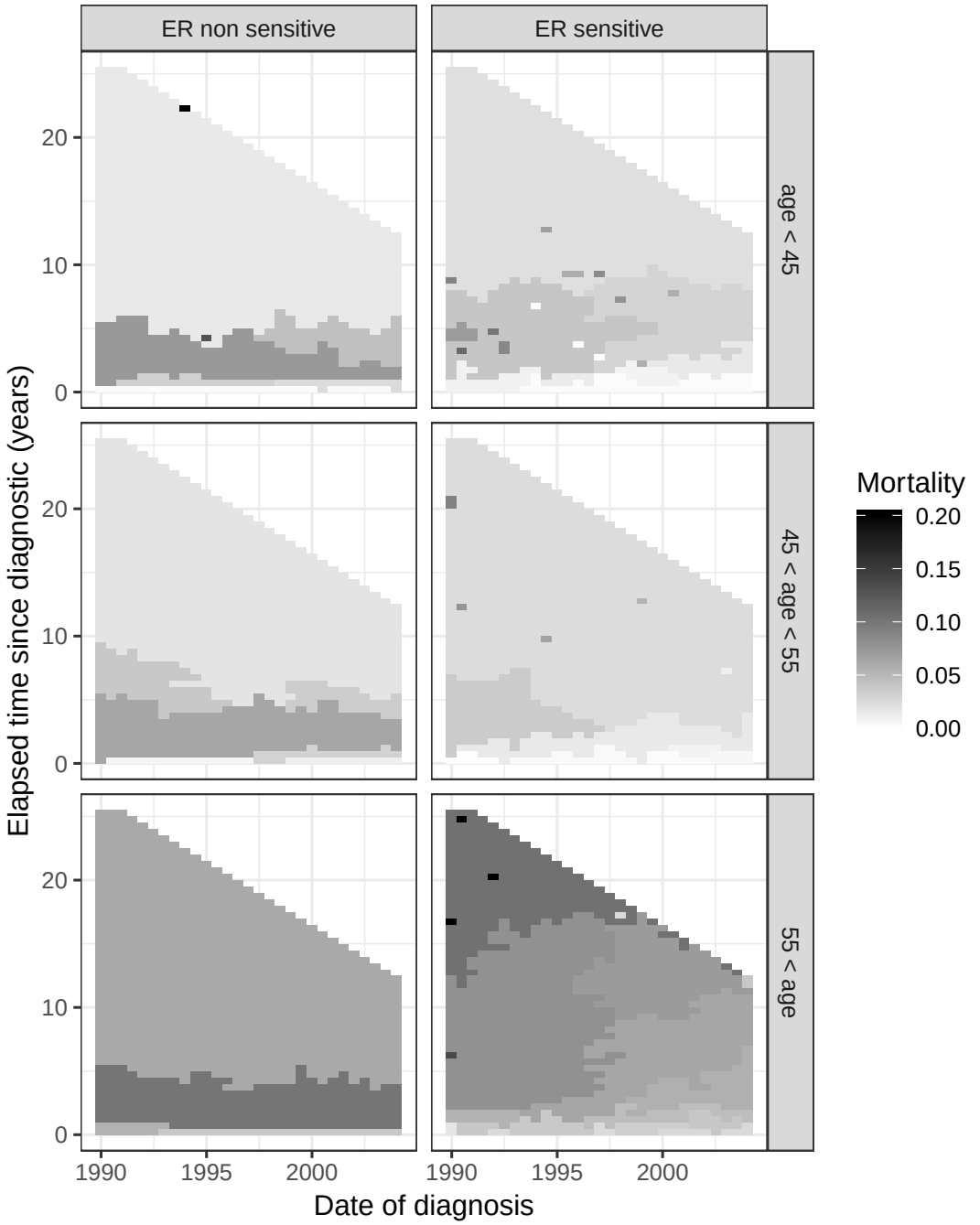

Figure 2: Estimated hazard of death since diagnosis of breast cancer for Stage 2 cancers. The estimation is carried separately for three classes of age at diagnosis: $(., 45]$, $(45, 55]$, and $(55, .)$ and for sensitive and non-sensitive estrogen receptor cancers. Inference is made with the L_0 regularization. All graphs share the same scale.

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