**Breast cancer risk factors and survival by tumour subtype: pooled analyses from the Breast Cancer Association Consortium**

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**Abstract** (240 words (max 250))

**Background:** It is not known if modifiable lifestyle factors that predict survival after invasive breast cancer (BC) differ by subtype.

**Methods:** We analysed data for 121 435 women diagnosed with BC from 67 studies in the Breast Cancer Association Consortium with 16 890 deaths (8 554 BC-specific) over 10 years. Cox regression was used to estimate associations between risk factors and 10-year all-cause mortality (primary analysis) and BC-specific mortality (secondary analysis) overall, by oestrogen receptor (ER) status, and by intrinsic-like subtype based on ER, progesterone receptor, human epidermal growth factor receptor 2, and grade.

**Results:** The strongest associations were between all-cause mortality and BMI ≥30 *vs* 18.5-25 kg/m2 [HR (95%CI): 1.19 (1.06,1.34)]; current *vs* never smoking [1.37 (1.27,1.47)], high *vs* low physical activity [0.43 (0.21,0.86)], age ≥30 years *vs* <20 years at first pregnancy [0.79 (0.72,0.86)]; >0 to <5 years *vs* ≥10 years since last full term birth (1.31 (1.11,1.55)); ever *vs* never use of oral contraceptives [0.91 (0.87,0.96)]; ever vs never use of menopausal hormone therapy, including current oestrogen-progestin therapy [0.61 (0.54,0.69)]. Similar associations with BC mortality were weaker; e.g. 1.11 (1.02, 1.21) for current *vs* never smoking). There was no strong evidence that these associations differed by ER status or intrinsic-like subtype.

**Conclusion:** Given the large dataset and lack of evidence that the detected associations between modifiable risk factors and 10-year mortality differed by subtype, these associations could be cautiously used in prognostication models to inform patient-centered care.

**Keywords**: breast cancer, survival, intrinsic-like subtypes, risk factors, all-cause mortality, breast cancer-specific mortality

**Key messages**

* In the largest dataset to date with 121 435 invasive breast cancer tumours from female breast cancer patients worldwide we studied the associations between 15 breast cancer risk factors and survival.
* Modifiable lifestyle factors, specifically obesity, smoking, and lack of physical activity, were associated with higher 10-year all-cause mortality; results of breast cancer-specific mortality were in line.
* There was no evidence to suggest differential associations between risk factors and survival by ER status or by intrinsic-like subtype.
* The associated risk factors could thus be used in prognostication models to inform patient-centred care without the need for subtype-specific considerations.

**Introduction**

Breast cancer is a heterogeneous disease with differing risk factors1 and aetiologies,2 and correspondingly differential response to treatment3 as well as prognosis.4 Despite the heterogeneous nature of breast cancer, there are few studies investigating possible differential relationships between risk factors and mortality according to tumour subtypes. Given that more women are surviving after a breast cancer diagnosis,5 identifying lifestyle and personal factors associated with mortality after breast cancer according to tumour subtypes is important.

A recent systematic literature review and meta-analysis in breast cancer patients6 concluded that there was limited suggestive evidence for physical activity, foods containing fibre, and foods containing soy being associated with decreased all-cause mortality, and for body fatness, weight gain, and intake of total fat and saturated fatty acids being associated with increased all-cause mortality. However, there was a lack of consistent data to draw conclusions for other dietary and nutritional risk factors regarding all-cause mortality or breast cancer-specific mortality, either overall or by molecular subtype.6

In a large population-based prospective cohort, cigarette smoking was found to be related to higher mortality from both breast cancer and smoking related diseases.7 Findings regarding reproductive factors have however been conflicting. Most studies have found no association between mortality after breast cancer and age at menarche,8-11 parity,10, 12-14 history of breastfeeding,11 duration of breastfeeding,11, 14 history of oral contraceptive use,10, 11, 15, 16 or duration of oral contraceptive use.11, 15-17 There are some reports of decreased mortality associated with younger age at menarche,18, 19 parity,20 history of breastfeeding,12, 21, 22 longer duration of breastfeeding,12 and menopausal hormone therapy (MHT).23, 24 Other studies have reported increased mortality associated with younger age at menarche,25 parity, particularly among women with luminal breast cancers26 and women diagnosed before age 50,13, 27 and a shorter time interval since last birth.8, 10, 11, 14, 26-30 There is paucity of data and no clear evidence for differential effects of the investigated risk factors with mortality for different intrinsic-like subtypes. A more detailed investigation is essential to improve our understanding of these relationships. Therefore, we aimed to investigate associations between prediagnosis reproductive and lifestyle risk factors on 10-year all-cause and breast cancer-specific mortality by tumour subtype of breast cancer patients. We also investigated whether prognostic models could be improved by inclusion of these factors.

**Methods**

**Study population and exposure assessment**

We employed data from studies participating in the Breast Cancer Association Consortium (BCAC), which are described in Supplementary Table S1. Details of the inclusion criteria are presented in the Supplementary Methods. The final study population consisted of 121 435 invasive, stage I-III, female breast cancer patients from 67 studies participating in the BCAC. All individual studies were approved by their appropriate institutional review boards and/or medical ethical committees. Written informed consent was obtained from all study subjects.

We focused on 15 breast cancer lifestyle and reproductive risk factors: age at menarche, parity, age at first full-term pregnancy (FFTP), time since last full term birth, ever breastfeeding, duration of breastfeeding, body mass index (BMI) (investigated both overall and separately within postmenopausal and pre/perimenopausal women), adult height, oral contraceptives (OC) use, menopausal hormone therapy (MHT) use, smoking status, pack-years of smoking, recent alcohol consumption, cumulative alcohol consumption, and physical activity. Exposure information was collected pre-diagnosis in nested case-control/prospective cohort studies and at or shortly after diagnosis in case-control studies and patient cohorts. Time since last full-term birth was calculated as the time interval between age at diagnosis and age at last full-term birth. Women were defined as postmenopausal if the last menstruation occurred >12 months before diagnosis, and as pre/perimenopausal otherwise. Menopausal status and MHT use were combined into a single variable with 8 categories, where former use was use more than 6 months prior to diagnosis and current use was use at date of diagnosis or within 6 months prior to date of diagnosis. Ever use of OC was defined as use for ≥4 months and never use as <4 four months of use. There were 3 categories for smoking status: never, former and current, with current defined as smoking in the last year before diagnosis. A pack-year constituted 20 cigarettes smoked per day for one year. Alcohol consumption and physical activity were based on the last year before diagnosis. For comparison with other studies, tertiles of physical activity (hours/week) were used. Cumulative alcohol consumption was that consumed over a lifetime until the date of diagnosis (Table 1).

**Breast cancer intrinsic-like subtypes**

The source of tumour marker data (i.e., data on expression of ER, PR, HER2, and grade) and assessment of specific tumour markers varied across the studies and included clinical/pathology records and immunohistochemistry (IHC) staining of whole tumour sections or tissue microarrays.31 Breast tumours were classified according to oestrogen receptor (ER) status (positive versus negative) and according to intrinsic-like subtypes based on ER, progesterone receptor (PR), the human epidermal growth factor receptor 2 (HER2), and grade.32

**Outcome assessment**

Vital status was ascertained by individual studies. Cause of death was coded according to the 10th revision of the International Classification of Diseases (ICD-10-WHO). The primary study outcome was 10-year all-cause mortality (death from any cause). The secondary outcome was 10-year breast cancer-specific mortality (death from breast cancer; coded as ICD-10-C50). Since all-cause mortality cannot be misclassified it is a more robust endpoint than breast cancer-specific mortality. In addition, there were more all-cause events than breast cancer-specific events also because not all studies coded cause of death, yielding greater power to detect associations of interest.

**Statistical analyses**

*Multiple imputation of missing data*

Multiple imputation, performed using R package MICE (version 2.30), was used to handle missing values of both risk factor and clinical-pathological variables as described in the Supplementary Methods. A list of imputed variables and corresponding percentages of missing values is provided in Supplementary Table S2.

*Associations of individual and multiple risk factors with all-cause and breast cancer-specific mortality overall and by subtype*

Delayed-entry Cox regression models were used to assess associations between lifestyle and reproductive breast cancer risk factors and 10-year all-cause and breast cancer mortality in all patients and by tumour subtypes according to ER status and intrinsic-like subtypes. Time-to-event started from date of diagnosis, and time-at-risk started from date of recruitment into the study if it was after date of diagnosis. Age of the patient was used as the time-scale so that patient age is implicitly accounted for without the need to estimate its coefficient.33 For breast cancer-specific mortality, women who died within 10 years from diagnosis and whose cause of death was not breast cancer or unknown were censored at age of death. Women who died 10 years or more after diagnosis were censored at their age at 10 years after diagnosis. All models were stratified by study and adjusted for tumour size, nodal status, tumour grade (except for luminal-B-HER2-negative-like), and systemic treatment (adjuvant endocrine therapy (yes/no), (neo)adjuvant chemotherapy (yes/no) and trastuzumab (yes/no)). Cox models were performed for each risk factor individually using imputed data (Table 2 and Supplementary Table S3), and as sensitivity analyses using complete-case data (Supplementary Table S4 and S5; Supplementary Figure S1 and S2). A Bonferroni corrected threshold of 3.7E-04 was considered for the p-values, as described in the Supplementary Methods.

Potential heterogeneity of the association estimates across tumour subtype was tested by means of a likelihood ratio test comparing models with and without an interaction term between the variable representing a specific risk factor and the variable representing the subtype (based on ER status only or according to the intrinsic-like classification) (Supplementary Table S6, Supplementary Methods).

To account for the interplay between risk factors, we fitted a single multivariable Cox regression model including all risk factors of interest (with the exception of pack-years) to assess associations with 10-year all-cause and breast cancer-specific mortality. Similar to analyses of individual risk factors with outcomes, the Cox model was stratified by study and adjusted for covariates as above. Since this analysis was performed in all patients, ER, PR and HER2 status were included as additional covariates.

The proportional hazards assumption was assessed for each risk factor of interest, based on all included cases, after applying exclusion criteria for individual subjects (not imputed). Plots of the Schoenfeld residuals did not show strong evidence of deviation from the proportional hazard assumption (data not shown).

Time-dependent ROC curve analyses were performed, as described in the Supplementary Methods, to assess whether the additional inclusion of the risk factors investigated would add discriminative power compared to a prognostic model based only on the established breast cancer prognostic factors.

**Results**

There were 16 890 deaths overall and 8554 breast cancer deaths after a follow-up time of 10 years in 121 435 breast cancer patients (Table 1). Overall median age at diagnosis was 57 years (IQR 48-65). Distribution of tumour and treatment characteristics and risk factors in all patients and by subtype is shown in Table 1.

*Associations of individual risk factors with all-cause and breast cancer-specific mortality* *overall and by subtype*

Associations of individual risk factors with all-cause mortality are shown in Table 2. Parous women had lower mortality compared to nulliparous, with strongest associations observed in women who had 1 (HR (95%CI): 0.87 (0.79, 0.96)) or 2 full-term pregnancies HR (95%CI): 0.86 (0.77, 0. 96). Among parous women, lower all-cause mortality was associated with later age at FFTP (P=1.0E-15), with HR of 0.79 (95%CI: (0.73, 0.86)) for women with FFTP at age ≥30 years compared to <20 years. Higher all-cause mortality was associated with a more recent full-term pregnancy only in women with ER+ tumours (time since last full-term birth 0-5 years versus ≥10 years HR (95%CI): 1.36 (1.12, 1.65)), but there was no statistical heterogeneity by ER status (P=3.3E-01; Supplementary Table S6).

Higher BMI was associated with higher all-cause mortality, particularly in postmenopausal women (P=1.8E-08), with HR of 1.20 (95%CI: 1.12, 1.29) for obese (≥30 kg/m2) women compared to normal weight women (BMI 18.5-25 kg/m2). Low BMI was likewise associated with higher all-cause mortality (HR 1.53 (95%CI: 1.30, 1.80) for underweight (BMI < 18.5 kg/m2) compared to normal weight.

Exogenous hormone exposure was associated with reduced all-cause mortality. Compared to never use, ever OC use was associated with decreased all-cause mortality (HR (95%CI): 0.88 (0.84, 0.93), P=2.3E-06). Overall, use of MHT was also associated with decreased risk of all-cause mortality, with the strongest association for current users of combined oestrogen and progesterone therapy compared to never users (HR (95%CI): 0.58 (0.52, 0.65)).

Current cigarette smoking compared to never smoking was associated with higher all-cause mortality (HR (95%CI): 1.38 (1.30, 1.45)). A 10-unit increase in the number of pack-years smoked was also associated with an increased risk of all-cause mortality (HR (95%CI): 1.11 (1.06, 1.15), P=2.0E-04). Physical activity was associated with decreased all-cause mortality (HR (95%CI): 0.42 (0.21, 0.85) for highest vs lowest tertile.

There was no evidence of heterogeneity by ER status or by intrinsic-like subtype (Table 2, Supplementary Table S6). Some variability was observed in estimates for women who had a recent full-term birth, especially comparing those 0-5 years to ≥10 years where HRs (95%CI) ranged from 1.55 (1.08, 2.24) for luminal A-like tumours to 0.93 (0.68, 1.27) for triple negative (TN) tumours, although there was no overall evidence of heterogeneity (P=6.8E-01).

Results of associations between single risk factors and breast cancer-specific mortality were generally in line with those observed for all-cause mortality but weaker (Supplementary Table S3). The exception was time since last full-term birth, where the association with breast cancer-specific mortality appeared to be somewhat stronger than with all-cause mortality, especially for the ER-positive (P=6.6E-06) and luminal A-like subtypes (P=2.4E-04). There was also some variability in the association estimates related to time since last full-term birth according to ER status (P=3.2E-02) and intrinsic-like subtype (P=9.7E-03), notably for last full-term birth 0-5 years versus ≥10 years prior to diagnosis for luminal A-like (HR (95%CI): 1.79 (1.27, 2.51)) compared to that for TN (HR (95%CI): 0.90 (0.65, 1.24)). Risk factors associated with all-cause mortality, such as parity, OC use, BMI in postmenopausal women, smoking, and physical activity were not associated with breast cancer-specific mortality after Bonferroni correction.

*Associations of multiple risk factors with all-cause and breast cancer-specific mortality* *overall*

Accounting for all risk factors simultaneously in the Cox model did not substantially change HRs for most risk factors (Table 3). Of the three individually-associated reproductive variables, parity was no longer associated with all-cause mortality after adjusting for age at FFTP and time since last full-term birth. Similar to results from individual risk factors and all-cause mortality, current use of combined oestrogen-progestin compared to never MHT use (HR (95%): 0.61 (0.54, 0.69)) and ever use of OC compared to never OC use (HR (95%): 0.91 (0.87, 0.96) were both still associated with all-cause mortality. All-cause mortality was increased in current smokers compared to non-smokers (HR (95%CI): 1.37 (1.27, 1.47). At least 5.5 hours/week of physical activity decreased risk of all-cause mortality (HR (95%CI): 0.43 (0.21, 0.86)) (highest *vs* lowest tertile)).

Associations of multiple risk factors with breast cancer-specific mortality (Supplementary Table S7) remained substantially unchanged compared to individual risk factors associations (Supplementary Table S3).

Sensitivity analyses relating to associations of multiple risk factors with outcomes restricted to the complete-case data yielded results that were generally in line with those of the imputed data analyses for both all-cause and breast cancer-specific mortality (data not shown).

*Evaluation of the discriminative power of the models*

Figure 1 and Supplementary Figure S3 show the area under the curve values over a range of ages for a Cox model only including classical prognostic factors (i.e. tumour characteristics and treatment) and for a Cox model additionally including the risk factors investigated. We observed a decrease in discriminative power of both models with older ages. The discriminative power of the model including additional risk factors was higher over all ages compared to that based on only classical prognostic factors. For all-cause mortality the concordance index increased from 0.69 to 0.71 when adding risk factors to the model (Figure 1). For breast cancer-specific mortality, the concordance index was 0.74 for both models (Supplementary Figure S3).

**Discussion**

Breast cancer risk factors for mortality after a breast cancer diagnosis according to tumour subtype have not been established. Identification and characterization of these associations is important since they may be useful for prognostication at the time of diagnosis. Therefore, our main objectives were to quantify associations between breast cancer risk factors and all-cause and breast cancer-specific mortality and to evaluate whether associations differ by tumour subtype. We found evidence for associations between modifiable lifestyle risk factors and all-cause mortality, namely, obesity, smoking, and physical activity as well as associations with reproductive risk factors, age at FFTP, and time since last birth, and exogenous hormone use in the form of OCs and MHTs. Similar associations were also found with breast cancer-specific mortality. After correction for multiple testing, there was no evidence for differential associations by ER status or intrinsic-like subtype.

Data on breast cancer risk factors in relation to survival according to tumour subtypes are scarce with a few studies reporting possibly differential associations between survival and older age at menarche,18, 34 breastfeeding,22 parity,26, 34 older age at FFTP,34 recent last birth,26 and low34 and high BMI34, 35 by tumour subtypes, and other studies reporting no differential associations with MHT use.36-38 Our data do not support the previous reports, which might have been chance findings.

Our findings indicate that several modifiable risk factors are associated with survival. Low and high BMI8, 10, 12, 34 as well as smoking7, 39 were found to increase both all-cause and breast cancer-specific mortality, while physical activity was found to decrease all-cause mortality40 with similar patterns of association for breast cancer-specific mortality.6 The observed associations with high BMI could, in part, be due to obese breast cancer survivors being less responsive to aromatase inhibitor treatments8, 41 or chemotherapy.8, 42, 43 A systematic review and meta-analysis also highlights evidence for a non-linear *J*-shaped dose-response relationship between BMI and mortality,44 consistent with findings from the current analysis that underweight women may also be at increased risk of mortality compared to normal weight women. The attenuated association between smoking and breast cancer-specific mortality compared to overall mortality could be attributed to the association of smoking with diseases other than breast cancer such as lung cancer and cardiovascular diseases. Comparable to results from two meta-analyses,6, 40 we found high physical activity to be associated with lower risk of all-cause mortality with similar patterns for breast cancer-specific mortality. Body weight, smoking, and physical activity are relevant breast cancer risk factors in that reduction in weight and smoking, as well as the promotion of physical activity are practical and useful targets for both patients and public health. The relevance of obesity and physical activity as modifiable factors is strengthened by growing evidence that postdiagnosis weight gain increases mortality in addition to prediagnosis BMI6, 45 and changes in pre- to postdiagnosis physical activity are also associated with mortality.6, 46

In line with previous literature, associations with age at menarche, number of full-term pregnancies, and breastfeeding with mortality were null after accounting for other reproductive variables.8, 10-12 Our data substantiate previously suggested patterns of association where risk of mortality decreases with older age at FFTP8, 10, 11, 34 and a more recent last birth increases mortality, particularly breast cancer-specific mortality.8, 13, 18, 28-30 The reasons for these associations are unclear. Women of higher socio-economic status often have their first child later and have better access to health care, lifestyle and nutrition, all of which can decrease mortality. The association of a more recent last birth with increased breast cancer-specific mortality appeared to be differential by ER status and intrinsic-like subtype, although not after accounting for multiple testing corrections. Two previous studies also found such associations only for luminal tumours.26, 29 Breast tumours occurring during pregnancy, post-partum, or during lactation can be subject to treatment and diagnosis delays, both of which may result in poorer prognosis.

Exposure to exogenous hormones – OC and MHT – was observed to be associated with decreased mortality irrespective of tumour subtype. Decreased all-cause mortality with ever OC use has been inconsistently reported8, 10, 15, 16 and may be due to differences in timing, duration, and dose of OCs. Ever MHT use was associated with decreased all-cause and breast cancer-specific mortality and corroborate the results from published meta-analyses.23, 24 On the other hand, current MHT use, particularly combined oestrogen-progestin, has been found to be associated with increased breast cancer-specific mortality in population-based prospective cohort studies,47, 48 but this estimate combines the joint effects of incidence and case-fatality. Our data confirm stronger associations of MHT use with all-cause mortality than with breast cancer-specific mortality, possibly due the importance of MHT use in influencing other comorbidities that lead to premature death. Unmeasured factors related to MHT such as differences in “health-seeking behaviour” and medical surveillance might be present, as women can only receive exogenous hormones after consultation with a physician, which could not be accounted for in this analysis, so that residual confounding cannot be excluded. Thus the observed association between MHT and survival does not imply that MHT use after diagnosis would be beneficial for survival, especially since it is well-established that MHT use increases risk of breast cancer.49

A major strength of our study is the sample size, making it the largest dataset of breast cancer patients available to date. Due to the large sample size, we were able to assess associations by ER and intrinsic-like subtype as well as heterogeneity between subtypes. We have collected and harmonized information on numerous potential risk factors and have fitted multivariable models that simultaneously accounted for established prognostic factors as well as first-line cancer treatment.

Despite centralized data harmonization, residual heterogeneity in the studies with varying designs and different coding of variables may still be present and affect our results. Timing of exposure information collection with respect to diagnosis also differs between study designs. Whereas prediagnosis information is generally collected prospectively in nested case-control/prospective cohort studies and retrospectively in case-control studies, patient cohort studies are more likely to collect postdiagnosis information. While some types of risk factor information such as current MHT use may be affected by whether they are assessed before or after diagnosis, this is less likely to be the case for most risk factors we considered, such as reproductive history, and BMI. In the current analysis, nine cohort studies provided risk factor information collected more than one year before diagnosis, comprising 11.4% of the total analysed sample. Their inclusion is not likely to have substantially affected our evaluation of associations between risk factors and survival also by tumour subtype. Delays in patient recruitment can lead to survival bias that we accounted for using delayed entry in the regression models, which if well-specified, should provide unbiased estimates.8 Another challenge was the large proportion of missing values for some of the variables under study. We addressed this issue by employing multiple imputation, which allowed us to keep the sample size intact and, if data are missing at random, should provide unbiased estimates for the associations of interest. Sensitivity analysis using complete-case data confirmed that for most variables, the results were in line with imputed results. While we have been able to investigate associations between numerous pertinent breast cancer risk factors with mortality, we were unable to consider others such as mode of detection and comorbidities, which may be relevant for mortality.

In conclusion, we provide evidence that associations of breast cancer risk factors with survival after a diagnosis of breast cancer are not differential by tumour subtype. The absence of effect heterogeneity by subtype suggests that the associated risk factors may be generalizable to all tumours, which facilitates their use in prognostication models and public health strategies without the need for subtype-specific considerations. The confirmed modifiable lifestyle risk factors for survival can empower breast cancer survivors and might be incorporated in patient-centred care to improve prognosis and quality of life.

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**Table 1. Characteristics of the breast cancer population based on data from 67 population-based and hospital-based studies.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Characteristic** | **Overall** | **ER+** | **ER-** | **Luminal A-like** | **Luminal B HER2-negative-like** | **Luminal B HER2-like** | **HER2-enriched-like** | **Triple negative** |
| **Number of women**a, n | 121 435 | 81 885 | 22 257 | 33 633 | 8915 | 7976 | 4025 | 8856 |
| **Number of overall deaths**, n | 16 890 | 9941 | 4587 | 3039 | 1490 | 1127 | 849 | 1858 |
| **Number of breast cancer specific deaths**, n | 8554 | 4654 | 2511 | 1256 | 792 | 613 | 458 | 978 |
| **Clinical risk factors** |  |  |  |  |  |  |  |  |
| **Age at diagnosis**, y, median (IQR)  Missing, n | 57 (48-65)  56 | 58 (49-66) | 53 (44-62) | 59 (50-67) | 56 (46-65) | 54 (45-64) | 54 (46-62) | 53 (44-63) |
| **Year of diagnosis**, n (%) |  |  |  |  |  |  |  |  |
| 1961-1975 | 264 (0.2) | 98 (0.1) | 105 (0.5) | 24 (0.1) | 3 (0.0) | 16 (0.2) | 19 (0.5) | 59 (0.7) |
| 1976-1990 | 4271 (3.6) | 1707 (2.2) | 931 (4.3) | 725 (2.2) | 273 (3.1) | 144 (1.8) | 188 (4.7) | 433 (5) |
| 1991-2005 | 68 872 (58.8) | 44 075 (55.6) | 13 425 (61.4) | 13 776 (41.8) | 3559 (40.7) | 3694 (47.4) | 2029 (51.1) | 4351 (49.8) |
| 2006-2019 | 43 725 (37.3) | 33 414 (42.1) | 7406 (33.9) | 18 465 (56.0) | 4905 (56.1) | 3943 (50.6) | 1734 (43.7) | 3898 (44.6) |
| Missing, n | 4303 |  |  |  |  |  |  |  |
| **Ethnicity**, n (%) |  |  |  |  |  |  |  |  |
| European | 91 981 (84) | 62 984 (84.7) | 15 479 (75.4) | 26 087 (85.8) | 6534 (82.5) | 5773 (77.2) | 2617 (68.3) | 6078 (76.7) |
| Hispanic American | 866 (0.8) | 554 (0.7) | 179 (0.9) | 225 (0.7) | 46 (0.6) | 78 (1.0) | 26 (0.7) | 104 (1.3) |
| African | 1015 (0.9) | 461 (0.6) | 435 (2.1) | 135 (0.4) | 52 (0.7) | 58 (0.8) | 52 (1.4) | 261 (3.3) |
| Asian | 13 139 (12.0) | 8397 (11.3) | 3991 (19.5) | 3033 (10.0) | 1090 (13.8) | 1416 (18.9) | 1061 (27.7) | 1263 (15.9) |
| Other | 2516 (2.3) | 1929 (2.6) | 433 (2.1) | 936 (3.1) | 198 (2.5) | 157 (2.1) | 77 (2.0) | 217 (2.7) |
| Missing, n | 11 918 |  |  |  |  |  |  |  |
| **Tumour size**, n (%) |  |  |  |  |  |  |  |  |
| ≤2 cm | 49 887 (61.5) | 36 848 (63.2) | 7746 (50.3) | 17 873 (65.5) | 3339 (46.0) | 3055 (52.2) | 1305 (44.6) | 3147 (48.2) |
| >2 and ≤5cm | 27 665 (34.1) | 19 024 (32.7) | 6706 (43.5) | 8358 (30.6) | 3449 (47.5) | 2478 (42.4) | 1374 (47.0) | 3016 (46.2) |
| >5 cm | 3603 (4.4) | 2388 (4.1) | 948 (6.2) | 1067 (3.9) | 472 (6.5) | 317 (5.4) | 245 (8.4) | 371 (5.7) |
| Missing, n | 40 280 |  |  |  |  |  |  |  |
| **Nodal status**, n (%) |  |  |  |  |  |  |  |  |
| Negative | 59 569 (62.1) | 43 212 (62.0) | 11 156 (59.6) | 20 203 (63.5) | 4352 (51.4) | 3930 (54.6) | 1795 (50.5) | 4874 (62.7) |
| Positive | 36 395 (37.9) | 26 476 (38.0) | 7551 (40.4) | 11 609 (36.5) | 4112 (48.6) | 3264 (45.4) | 1759 (49.5) | 2905 (37.3) |
| Missing, n | 25 471 |  |  |  |  |  |  |  |
| **Tumour stage**, n (%) |  |  |  |  |  |  |  |  |
| I | 34 157 (44.5) | 25 351 (45.9) | 5147 (34.6) | 12 222 (47.7) | 1903 (29.4) | 2209 (37.5) | 839 (28.0) | 2143 (34.6) |
| II | 34 696 (45.2) | 24 498 (44.3) | 7663 (51.5) | 11 154 (43.5) | 3567 (55.2) | 2838 (48.1) | 1561 (52.1) | 3314 (53.5) |
| III | 7990 (10.4) | 5411 (9.8) | 2056 (13.8) | 2243 (8.8) | 997 (15.4) | 850 (14.4) | 597 (19.9) | 742 (12) |
| Missing, n | 44 592 |  |  |  |  |  |  |  |
| **Grade**, n (%) |  |  |  |  |  |  |  |  |
| Grade 1 | 17 919 (19.2) | 15 546 (22.6) | 800 (4.5) | 10 130 (30.1%) | - | 672 (9.3) | 62 (1.8) | 279 (3.7) |
| Grade 2 | 45 065 (48.3) | 37 347 (54.3) | 4614 (26.1) | 23 503 (69.9%) | - | 3397 (47.0) | 918 (26.4) | 1709 (22.4) |
| Grade 3 | 30 231 (32.4) | 15 852 (23.1) | 12 253 (69.4) | - | 8915 (100%) | 3151 (43.6) | 2498 (71.8) | 5651 (74) |
| Missing, n | 28 220 |  |  |  |  |  |  |  |
| **Surgery**, n (%) |  |  |  |  |  |  |  |  |
| No surgery | 1160 (1.6) | 437 (0.8) | 152 (1.1) | 108 (0.4) | 26 (0.4) | 37 (0.7) | 22 (0.8) | 35 (0.6) |
| Breast conserving surgery | 29 530 (40.9) | 22 923 (44.4) | 4971 (36.8) | 11 551 (47.5) | 2371 (36.7) | 2188 (40.3) | 775 (28.9) | 2168 (38.8) |
| Mastectomy | 22 785 (31.6) | 16 032 (31.1) | 5237 (38.7) | 6730 (27.7) | 2156 (33.4) | 2092 (38.5) | 1378 (51.3) | 1821 (32.6) |
| Type unknown | 18 677 (25.9) | 12 187 (23.6) | 3155 (23.3) | 5942 (24.4) | 1907 (29.5) | 1111 (20.5) | 510 (19.0) | 1561 (27.9) |
| Missing, n | 49 283 |  |  |  |  |  |  |  |
| **Radiation therapy**, n (%) |  |  |  |  |  |  |  |  |
| No | 18 563 (27.6) | 12 525 (26.3) | 3684 (28.8) | 5268 (25.7) | 1250 (22.8) | 1353 (26.1) | 801 (30.8) | 1217 (25.7) |
| Yes | 48 616 (72.4) | 35 037 (73.7) | 9111 (71.2) | 15 241 (74.3) | 4243 (77.2) | 3826 (73.9) | 1797 (69.2) | 3510 (74.3) |
| Missing, n | 54 256 |  |  |  |  |  |  |  |
| **Chemotherapy**, n (%) |  |  |  |  |  |  |  |  |
| No | 27 667 (41) | 21 895 (45.9) | 2310 (16.5) | 11 812 (53.0) | 1632 (25.3) | 1203 (21.9) | 328 (11.3) | 864 (15.2) |
| Yes | 39 815 (59) | 25 796 (54.1) | 11 729 (83.5) | 10 465 (47.0) | 4820 (74.7) | 4294 (78.1) | 2584 (88.7) | 4816 (84.8) |
| Missing, n | 53 953 |  |  |  |  |  |  |  |
| **Endocrine therapy,** n (%) |  |  |  |  |  |  |  |  |
| No | 19 688 (28.6) | 7869 (15.6) | 9232 (77.4) | 3629 (15.5) | 781 (13.1) | 978 (17.2) | 2209 (88.0) | 3907 (84.5) |
| Yes | 49 163 (71.4) | 42 682 (84.4) | 2689 (22.6) | 19 859 (84.5) | 5175 (86.9) | 4702 (82.8) | 302 (12.0) | 717 (15.5) |
| Missing, n | 52 584 |  |  |  |  |  |  |  |
| **Trastuzumab**, n (%) |  |  |  |  |  |  |  |  |
| No | 50 545 (95.1) | 33 531 (95.4) | 10 337 (91.6) | 16 909 (99.7) | 4849 (99.4) | 2341 (60.9) | 1306 (61.9) | 5104 (99.6) |
| Yes | 2598 (4.9) | 1607 (4.6) | 952 (8.4) | 53 (0.3) | 30 (0.6) | 1505 (39.1) | 805 (38.1) | 18 (0.4) |
| Missing, n | 68 292 |  |  |  |  |  |  |  |
| **Reproductive and lifestyle risk factors** |  |  |  |  |  |  |  |  |
| **Age at menarche**, median (IQR)  Missing, n | 13 (12-14)  35 355 | 13 (12-14) | 13 (12-14) | 13 (12-14) | 13 (12-14) | 13 (12-14) | 13 (12-14) | 13 (12-14) |
| **Parity**, median (IQR) | 2 (1-3) | 2 (1-3) | 2 (1-3) | 2 (1-3) | 2 (1-3) | 2 (1-3) | 2 (1-3) | 2 (1-3) |
| Nulliparous, n (%) | 12 932 (14) | 8971 (14.2) | 2066 (12.9) | 3633 (14.1) | 934 (15) | 870 (15) | 384 (13.5) | 787 (12.8) |
| Parous, n (%) | 79 415 (86) | 54 292 (85.8) | 13 955 (87.1) | 22 162 (85.9) | 5291 (85) | 4928 (85) | 2456 (86.5) | 5376 (87.2) |
| Missing, n | 29 088 |  |  |  |  |  |  |  |
| **Age at first full term pregnancy**b, median (IQR), missing, n | 25 (22-28)  50 965 | 25 (22-28) | 24 (21-28) | 24 (21-28) | 25 (22-28) | 25 (22-29) | 25 (22-28) | 24 (21-27) |
| **Breastfeeding**, n (%) |  |  |  |  |  |  |  |  |
| Never | 24 906 (39.5) | 16 660 (38.4) | 4476 (39.9) | 7039 (39.2) | 1754 (41.9) | 1716 (40.2) | 831 (41.3) | 1796 (42.5) |
| Ever | 38 195 (60.5) | 26 730 (61.6) | 6734 (60.1) | 10 912 (60.8) | 2435 (58.1) | 2555 (59.8) | 1181 (58.7) | 2433 (57.5) |
| Missing, n | 58 334 |  |  |  |  |  |  |  |
| Duration in monthsc, median (IQR) | 7 (3-15) | 7 (3-15) | 7 (3-16) | 7.1 (3-15) | 7 (3-15.05) | 7 (3-15) | 8 (3-17) | 6.1 (3-15) |
| Missing, n | 68 870 |  |  |  |  |  |  |  |
| **Time since last full term birth**b, n (%) |  |  |  |  |  |  |  |  |
| ≥ 10 years | 29 200 (64.2) | 18 626 (63.3) | 5795 (65.7) | 7901 (65.5) | 1822 (62) | 1986 (63) | 1096 (67.8) | 2303 (67.3) |
| 5 - 10 years | 1926 (4.2) | 1115 (3.8) | 466 (5.3) | 362 (3.0) | 103 (3.5) | 177 (5.6) | 65 (4.0) | 163 (4.8) |
| 0 - 5 years | 1179 (2.6) | 601 (2.0) | 393 (4.5) | 161 (1.3) | 70 (2.4) | 101 (3.2) | 51 (3.2) | 130 (3.8) |
| ≤ 0 years | 223 (0.5) | 89 (0.3) | 95 (1.1) | 14 (0.1) | 12 (0.4) | 20 (0.6) | 20 (1.2) | 37 (1.1) |
| Missing, n | 75 975 |  |  |  |  |  |  |  |
| **Oral contraceptives**, n (%) |  |  |  |  |  |  |  |  |
| Never use | 29 677 (44.5) | 20 263 (45) | 5090 (43.4) | 8398 (46.4) | 1967 (45.1) | 2018 (43.6) | 1096 (48.6) | 1923 (43.2) |
| Ever use | 37 070 (55.5) | 24 799 (55) | 6629 (56.6) | 9701 (53.6) | 2395 (54.9) | 2608 (56.4) | 1159 (51.4) | 2533 (56.8) |
| Missing, n | 54 688 |  |  |  |  |  |  |  |
| **Menopausal hormone therapy**, n (%) |  |  |  |  |  |  |  |  |
| Never use, postmenopausal | 28 534 (37.1) | 20 062 (38.3) | 5088 (37.1) | 9129 (41.4) | 2315 (42.8) | 2044 (39) | 1108 (43.3) | 2115 (39.0) |
| Formere use oestrogen therapy | 1394 (1.8) | 1041 (2) | 195 (1.4) | 397 (1.8) | 81 (1.5) | 77 (1.5) | 40 (1.6) | 91 (1.7) |
| Formere use oestrogen+progestin | 1414 (1.8) | 1035 (2) | 246 (1.8) | 490 (2.2) | 91 (1.7) | 94 (1.8) | 49 (1.9) | 124 (2.3) |
| Formere use (unknown type) | 5972 (7.8) | 4366 (8.3) | 912 (6.7) | 1960 (8.9) | 481 (8.9) | 291 (5.6) | 164 (6.4) | 405 (7.5) |
| Currentf use oestrogen therapy | 2175 (2.8) | 1456 (2.8) | 272 (2.0) | 562 (2.5) | 103 (1.9) | 129 (2.5) | 48 (1.9) | 119 (2.2) |
| Currentf use oestrogen+progestin | 3755 (4.9) | 2689 (5.1) | 458 (3.3) | 1251 (5.7) | 181 (3.3) | 287 (5.5) | 79 (3.1) | 205 (3.8) |
| Currentf use (unknown type) | 5854 (7.6) | 4398 (8.4) | 647 (4.7) | 1896 (8.6) | 300 (5.5) | 247 (4.7) | 102 (4) | 236 (4.4) |
| Pre/perimenopausal | 27 790 (36.1) | 17 325 (33.1) | 5888 (43.0) | 6390 (28.9) | 1855 (34.3) | 2067 (39.5) | 971 (37.9) | 2122 (39.2) |
| Missing, n | 44 547 |  |  |  |  |  |  |  |
| **BMI**d, median (IQR) | 25 (23-28) | 25 (23-29) | 25 (22-28) | 25 (23-29) | 26 (23-29) | 25 (22-28) | 25 (22-28) | 25 (23-29) |
| 18.5-25 kg/m2, n (%) | 43 302 (47.4) | 29 382 (46.9) | 7716 (47.9) | 11 545 (44.2) | 2813 (42.8) | 2962 (49.4) | 1428 (49.4) | 2925 (45.8) |
| <18.5 kg/m2, n (%) | 1657 (1.8) | 1103 (1.8) | 355 (2.2) | 405 (1.6) | 117 (1.8) | 143 (2.4) | 72 (2.5) | 132 (2.1) |
| 25-30 kg/m2, n (%) | 29 960 (32.8) | 20 776 (33.2) | 5134 (31.9) | 8939 (34.2) | 2210 (33.6) | 1857 (31.0) | 933 (32.3) | 2041 (32) |
| >=30 kg/m2, n (%) | 16 435 (18.0) | 11 353 (18.1) | 2891 (18) | 5228 (20.0) | 1430 (21.8) | 1034 (17.2) | 459 (15.9) | 1284 (20.1) |
| Missing, n | 30 081 |  |  |  |  |  |  |  |
| **Adult height**, median (IQR) | 163 (158-168) | 163 (159-168) | 163 (158-168) | 163 (159-168) | 163 (158-168) | 163 (158-168) | 162 (157-167) | 163 (158-168) |
| Missing, n | 33 481 |  |  |  |  |  |  |  |
| **Smoking,** n (%) |  |  |  |  |  |  |  |  |
| Never | 39 512 (59.0) | 27 175 (59.3) | 7352 (63.3) | 11 767 (60.1) | 2795 (62.4) | 2961 (64.3) | 1581 (68.7) | 2856 (64.0) |
| Formerg | 17 407 (26.0) | 12 082 (26.3) | 2424 (20.9) | 4954 (25.3) | 1093 (24.4) | 1069 (23.2) | 387 (16.8) | 903 (20.2) |
| Currenth | 10 073 (15.0) | 6605 (14.4) | 1840 (15.8) | 2850 (14.6) | 589 (13.2) | 575 (12.5) | 332 (14.4) | 701 (15.7) |
| Missing, n | 54 443 |  |  |  |  |  |  |  |
| Pack-years of smoking |  |  |  |  |  |  |  |  |
| Former smokersg, median (IQR) | 0.8 (0.3-1.8) | 0.8 (0.3-1.8) | 0.7 (0.2-1.6) | 0.9 (0.3-1.9) | 0.8 (0.2-1.8) | 0.7 (0.2-1.8) | 0.6 (0.2-1.7) | 0.7 (0.2-1.6) |
| Current smokersh, median (IQR) | 1.9 (0.9-3.1) | 1.9 (1.0-3.1) | 1.5 (0.7-2.6) | 2.0 (0.9-3.2) | 2.0 (1.0-3.1) | 1.6 (0.7-2.5) | 1.6 (0.8-2.7) | 1.5 (0.6-2.6) |
| Missing, n | 62 214 |  |  |  |  |  |  |  |
| **Alcohol consumption**h |  |  |  |  |  |  |  |  |
| g/week, median (IQR)  Missing, n  **Cumulative alcohol consumption** | 14.7 (0.0-57.3)  100 522 | 16.0 (0.0-59.5) | 10.8 (0.0-50.7) | 12.0 (0.0-51.8) | 12.0 (0.0-49.7) | 15.0 (0.0-60.0) | 6.0 (0.0-48.3) | 6.0 (0.0-45.0) |
| g/day, median (IQR)  Missing, n | 1.9 (0.0-7.9)  102 451 | 2.0 (0.0-8.2) | 1.1 (0.0-6.1) | 2.0 (0.0-8.4) | 1.7 (0.0-7.0) | 2.1 (0.0-7.8) | 0.8 (0.0-5.6) | 1.0 (0.0-5.7) |
| **Physical activity**h,i , median (IQR) | 3 (1-8) | 3 (1-9) | 3 (1-8) | 5 (1-11) | 4 (2-11) | 4 (1-9) | 4 (1-9) | 4 (1-10) |
| < 1.8 hours/week, n (%) | 7103 (33.3) | 4643 (31.6) | 1043 (31.1) | 1564 (27.1) | 305 (24.6) | 437 (28.2) | 222 (29.1) | 418 (31.0) |
| ≥ 1.8 - < 5.5 hours/week, n (%) | 7063 (33.1) | 4679 (31.9) | 1106 (33.0) | 1545 (26.8) | 424 (34.2) | 491 (31.7) | 231 (30.4) | 382 (28.3) |
| ≥ 5.5 hours/week, n (%) | 7154 (33.6) | 5363 (36.5) | 1205 (35.9) | 2656 (46.1) | 510 (41.2) | 619 (40.1) | 308 (40.5) | 549 (40.7) |
| Missing, n | 100 115 |  |  |  |  |  |  |  |

Percentages shown in the table might not sum up to 100% due to rounding. a Numbers for subtypes do not add to total due to missing. b For parous women only. c For women who breastfed only. d BMI at interview. e More than 6 months before diagnosis. f At diagnosis or within 6 months before diagnosis. g More than 1 year before diagnosis. h At diagnosis or within 1 year before diagnosis. I Categories based on the tertiles of the observed distribution of the variable.

**Table 2. Associations between individual risk factors and 10 years all-cause mortality by ER status and intrinsic-like subtype based on the imputed datasets.**

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Risk factor** | **Overall** | **ER+** | **ER-** | **Luminal A-like** | **Luminal B HER2-negative-like** | **Luminal B HER2-like** | **HER2-enriched-like** | **Triple negative** |
| **P**  **HR [95% CI]** | **P**  **HR [95% CI]** | **P**  **HR [95% CI]** | **P**  **HR [95% CI]** | **P**  **HR [95% CI]** | **P**  **HR [95% CI]** | **P**  **HR [95% CI]** | **P**  **HR [95% CI]** |
| **Age at menarche**, per 1 year increase | 1.2E-01  1.02 [1.00,1.04] | 4.1E-01  1.01 [0.99,1.03] | 3.0E-02  1.03 [1.00,1.06] | 8.5E-01  1.00 [0.98,1.03] | 5.4E-01  1.01 [0.98,1.04] | 1.3E-01  1.03 [0.99,1.07] | 1.3E-01  1.04 [0.99,1.09] | 1.1E-01  1.03 [0.99,1.07] |
| **Parity** | 2.5E-04 | 1.5E-05 | 7.2E-02 | 1.1E-04 | 6.1E-02 | 4.5E-01 | 8.7E-01 | 2.0E-02 |
| 0 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 1 | 0.87 [0.79,0.96] | 0.87 [0.79,0.97] | 0.85 [0.73,0.98] | 0.86 [0.75,0.99] | 0.88 [0.76,1.02] | 0.91 [0.75,1.11] | 0.87 [0.66,1.15] | 0.80 [0.67,0.96] |
| 2 | 0.86 [0.77,0.96] | 0.83 [0.74,0.93] | 0.92 [0.80,1.06] | 0.81 [0.70,0.93] | 0.86 [0.73,1.01] | 0.87 [0.71,1.06] | 1.00 [0.76,1.31] | 0.84 [0.71,1.00] |
| 3 | 0.90 [0.82,1.00] | 0.88 [0.79,0.98] | 0.92 [0.79,1.06] | 0.86 [0.76,0.98] | 0.90 [0.77,1.06] | 0.92 [0.74,1.14] | 0.97 [0.75,1.25] | 0.86 [0.71,1.05] |
| 4+ | 0.97 [0.88,1.06] | 0.92 [0.83,1.02] | 1.05 [0.90,1.23] | 0.89 [0.78,1.02] | 0.94 [0.79,1.12] | 1.01 [0.80,1.29] | 1.06 [0.80,1.41] | 0.99 [0.80,1.24] |
| **Age at first full term pregnancy**a, years | 1.0E-15 | 1.5E-12 | 3.9E-03 | 3.4E-08 | 8.3E-03 | 9.5E-04 | 3.9E-01 | 1.3E-02 |
| < 20 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| 20 to < 25 | 0.88 [0.83,0.94] | 0.86 [0.80,0.93] | 0.93 [0.83,1.04] | 0.84 [0.76,0.93] | 0.92 [0.80,1.07] | 0.83 [0.69,1.00] | 0.94 [0.71,1.23] | 0.91 [0.79,1.04] |
| 25 to < 30 | 0.82 [0.76,0.87] | 0.80 [0.73,0.86] | 0.87 [0.77,0.99] | 0.78 [0.70,0.87] | 0.82 [0.71,0.95] | 0.79 [0.65,0.97] | 0.89 [0.67,1.17] | 0.86 [0.73,1.01] |
| ≥ 30 | 0.79 [0.73,0.86] | 0.78 [0.71,0.87] | 0.82 [0.71,0.96] | 0.79 [0.68,0.91] | 0.83 [0.70,1.00] | 0.73 [0.58,0.91] | 0.80 [0.58,1.10] | 0.82 [0.69,0.98] |
| **Time since last full term birth**a**,** years | 3.8E-02 | 5.9E-05 | 6.3E-01 | 2.2E-03 | 6.4E-01 | 9.9E-02 | 6.9E-01 | 4.7E-01 |
| ≥ 10 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| ≥ 5 - < 10 | 1.07 [0.96,1.19] | 1.15 [1.01,1.33] | 0.95 [0.81,1.12] | 1.16 [0.98,1.38] | 1.10 [0.83,1.45] | 1.17 [0.92,1.50] | 0.99 [0.73,1.34] | 0.88 [0.70,1.10] |
| > 0 - < 5 | 1.21 [1.03,1.41] | 1.36 [1.12,1.65] | 1.02 [0.82,1.26] | 1.55 [1.08,2.24] | 1.11 [0.83,1.48] | 1.28 [0.86,1.91] | 1.07 [0.76,1.51] | 0.93 [0.68,1.27] |
| ≤ 0 | 1.15 [0.90,1.47] | 1.48 [1.14,1.90] | 0.83 [0.56,1.22] | 1.66 [1.05,2.61] | 1.19 [0.79,1.78] | 1.48 [0.97,2.26] | 0.72 [0.39,1.36] | 0.76 [0.43,1.35] |
| **Breastfeeding**a |  |  |  |  |  |  |  |  |
| Per 6 months increase | 1.3E-01  1.02 [0.99,1.04] | 3.6E-01  1.01 [0.99,1.04] | 5.0E-02  1.03 [1.00,1.06] | 3.0E-01  1.01 [0.99,1.04] | 5.8E-01  1.01 [0.97,1.06] | 2.5E-01  1.02 [0.99,1.06] | 5.2E-01  1.01 [0.97,1.05] | 4.7E-02  1.03 [1.00,1.06] |
| Ever vs never | 6.2E-01  0.97 [0.85,1.10] | 4.3E-01  0.95 [0.84,1.08] | 8.9E-01  1.01 [0.84,1.23] | 3.3E-01  0.93 [0.81,1.08] | 8.9E-01  0.99 [0.83,1.17] | 5.9E-01  0.94 [0.76,1.17] | 9.5E-01  0.99 [0.75,1.31] | 8.2E-01  1.02 [0.85,1.22] |
| **BMI**, kg/m2 |  |  |  |  |  |  |  |  |
| **All women** | 6.2E-03 | 1.4E-03 | 1.6E-01 | 1.4E-03 | 6.2E-02 | 7.9E-02 | 4.7E-01 | 1.9E-01 |
| 18.5 to < 25 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| < 18.5 | 1.34 [0.96,1.87] | 1.41 [1.03,1.95] | 1.24 [0.82,1.87] | 1.56 [1.12,2.18] | 1.32 [0.80,2.18] | 1.17 [0.71,1.94] | 1.22 [0.69,2.14] | 1.20 [0.78,1.83] |
| 25 to < 30 | 1.05 [0.92,1.21] | 1.06 [0.94,1.20] | 1.03 [0.86,1.24] | 1.03 [0.90,1.18] | 1.07 [0.92,1.26] | 1.13 [0.96,1.33] | 0.98 [0.80,1.20] | 1.04 [0.86,1.27] |
| ≥ 30 | 1.23 [1.09,1.40] | 1.24 [1.10,1.39] | 1.20 [1.01,1.43] | 1.24 [1.09,1.41] | 1.22 [1.04,1.42] | 1.23 [1.01,1.50] | 1.19 [0.92,1.55] | 1.21 [1.02,1.43] |
| **Postmenopausal women** | 1.8E-08 | 3.0E-07 | 5.6E-03 | 1.2E-06 | 5.2E-02 | 1.3E-01 | 3.4E-01 | 5.4E-02 |
| 18.5 to < 25 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| < 18.5 | 1.53 [1.30,1.80] | 1.57 [1.30,1.89] | 1.46 [1.09,1.95] | 1.73 [1.41,2.12] | 1.45 [0.89,2.38] | 1.16 [0.67,2.00] | 1.42 [0.80,2.50] | 1.48 [1.03,2.13] |
| 25 to < 30 | 1.05 [0.97,1.12] | 1.06 [0.97,1.15] | 1.02 [0.92,1.12] | 1.02 [0.92,1.12] | 1.09 [0.94,1.26] | 1.16 [0.95,1.42] | 0.95 [0.75,1.20] | 1.02 [0.89,1.17] |
| ≥ 30 | 1.20 [1.12,1.29] | 1.22 [1.12,1.33] | 1.15 [1.02,1.29] | 1.21 [1.09,1.35] | 1.20 [1.00,1.44] | 1.20 [0.97,1.48] | 1.19 [0.92,1.53] | 1.14 [0.98,1.33] |
| **Pre/perimenopausal women** | 3.7E-01 | 3.5E-01 | 5.4E-01 | 4.8E-01 | 4.5E-01 | 4.5E-01 | 9.0E-01 | 5.2E-01 |
| 18.5 to < 25 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| < 18.5 | 1.08 [0.53,2.21] | 1.14 [0.54,2.41] | 1.03 [0.49,2.19] | 1.17 [0.49,2.80] | 1.17 [0.54,2.52] | 1.17 [0.46,2.95] | 1.02 [0.41,2.55] | 0.90 [0.36,2.22] |
| 25 to < 30 | 1.07 [0.76,1.49] | 1.06 [0.77,1.48] | 1.06 [0.72,1.57] | 1.08 [0.70,1.66] | 1.04 [0.76,1.41] | 1.06 [0.76,1.49] | 1.02 [0.71,1.47] | 1.09 [0.68,1.74] |
| ≥ 30 | 1.32 [0.94,1.85] | 1.32 [0.96,1.82] | 1.30 [0.88,1.94] | 1.36 [0.87,2.12] | 1.28 [0.96,1.72] | 1.34 [0.94,1.92] | 1.18 [0.75,1.88] | 1.35 [0.90,2.04] |
| **Adult height**, per 5 cm increase | 2.2E-01  0.97 [0.92,1.02] | 2.9E-01  0.97 [0.91,1.03] | 1.7E-01  0.97 [0.92,1.02] | 2.5E-01  0.97 [0.91,1.03] | 5.1E-01  0.98 [0.91,1.05] | 4.7E-01  0.97 [0.90,1.05] | 2.0E-01  0.95 [0.87,1.03] | 2.8E-01  0.97 [0.92,1.03] |
| **Oral contraceptive use** | 2.3E-06 | 4.4E-05 | 4.4E-03 | 1.1E-04 | 8.4E-02 | 7.0E-02 | 1.4E-01 | 9.4E-03 |
| Ever vs never | 0.88 [0.84,0.93] | 0.89 [0.84,0.94] | 0.88 [0.80,0.96] | 0.87 [0.81,0.93] | 0.91 [0.81,1.03] | 0.89 [0.79,1.01] | 0.90 [0.77,1.04] | 0.88 [0.78,0.98] |
| **Menopausal hormone therapy** | 0.0E+00 | 0.0E+00 | 2.0E-10 | 0.0E+00 | 6.4E-06 | 3.9E-05 | 1.3E-02 | 7.6E-04 |
| Never use, postmenopausal | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| Formerb use of ET | 0.73 [0.64,0.84] | 0.75 [0.65,0.88] | 0.67 [0.48,0.93] | 0.78 [0.64,0.94] | 0.68 [0.49,0.94] | 0.75 [0.50,1.13] | 0.60 [0.27,1.31] | 0.71 [0.46,1.10] |
| Formerb use of EPT | 0.81 [0.70,0.93] | 0.80 [0.67,0.95] | 0.89 [0.68,1.18] | 0.75 [0.57,0.99] | 0.86 [0.58,1.27] | 0.77 [0.49,1.19] | 0.97 [0.55,1.70] | 0.93 [0.64,1.35] |
| Formerb use (unknown type) | 0.80 [0.75,0.85] | 0.79 [0.74,0.85] | 0.81 [0.71,0.94] | 0.78 [0.70,0.86] | 0.82 [0.68,1.01] | 0.79 [0.63,0.99] | 0.87 [0.66,1.15] | 0.80 [0.68,0.94] |
| Currentc use of ET | 0.70 [0.61,0.79] | 0.68 [0.59,0.79] | 0.75 [0.58,0.97] | 0.73 [0.60,0.88] | 0.64 [0.42,0.97] | 0.64 [0.42,0.95] | 0.53 [0.29,0.99] | 0.83 [0.59,1.17] |
| Currentc use of EPT | 0.58 [0.52,0.65] | 0.59 [0.52,0.67] | 0.56 [0.45,0.70] | 0.59 [0.50,0.70] | 0.57 [0.40,0.82] | 0.55 [0.40,0.76] | 0.53 [0.34,0.84] | 0.64 [0.48,0.85] |
| Currentc use (unknown type) | 0.75 [0.69,0.82] | 0.72 [0.65,0.80] | 0.87 [0.71,1.06] | 0.72 [0.64,0.82] | 0.70 [0.56,0.88] | 0.72 [0.53,0.99] | 0.81 [0.54,1.23] | 0.96 [0.73,1.27] |
| Pre/perimenopausal | 0.88 [0.82,0.94] | 0.94 [0.85,1.03] | 0.81 [0.72,0.91] | 0.97 [0.86,1.10] | 0.87 [0.75,1.01] | 0.87 [0.72,1.06] | 0.83 [0.67,1.03] | 0.83 [0.71,0.96] |
| **Smoking** | 0.0E+00 | 0.0E+00 | 7.0E-04 | 0.0E+00 | 7.5E-04 | 9.6E-03 | 7.7E-02 | 1.7E-02 |
| Never | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| Formerd | 1.01 [0.97,1.05] | 1.04 [0.98,1.09] | 0.97 [0.88,1.06] | 1.05 [0.98,1.13] | 0.99 [0.89,1.12] | 1.00 [0.88,1.14] | 1.07 [0.86,1.33] | 0.94 [0.83,1.05] |
| Currente | 1.38 [1.30,1.45] | 1.46 [1.37,1.56] | 1.20 [1.10,1.32] | 1.59 [1.48,1.71] | 1.31 [1.14,1.50] | 1.28 [1.09,1.50] | 1.28 [1.04,1.59] | 1.20 [1.04,1.37] |
| **No. of pack-years of smoking,** per 10 units increase | 2.0E-04  1.11 [1.06,1.15] | 2.2E-04  1.12 [1.07,1.17] | 5.7E-04  1.08 [1.04,1.12] | 7.0E-05  1.13 [1.08,1.18] | 6.7E-03  1.10 [1.03,1.16] | 5.2E-03  1.09 [1.03,1.15] | 6.5E-03  1.10 [1.03,1.17] | 6.5E-03  1.07 [1.03,1.12] |
| **Alcohol consumption**e**,** per 10g/week | 8.0E-01  1.01 [0.99,1.01] | 8.3E-01  1.00 [0.99,1.01] | 8.0E-01  1.00 [0.99,1.01] | 9.9E-01  1.00 [0.99,1.01] | 7.4E-01  1.00 [0.99,1.01] | 6.3E-01  1.00 [0.98,1.01] | 9.0E-01  1.00 [0.99,1.02] | 7.1E-01  1.00 [0.98,1.01] |
| **Cumulative alcohol consumption,** per 10g/day | 6.9E-01  1.01 [0.96,1.06] | 6.6E-01  1.01 [0.96,1.06] | 7.7E-01  1.01 [0.96,1.06] | 6.3E-01  1.01 [0.96,1.07] | 8.2E-01  1.01 [0.94,1.08] | 8.7E-01  1.01 [0.95,1.06] | 5.4E-01  1.02 [0.96,1.08] | 8.8E-01  1.00 [0.94,1.07] |
| **Physical activitye,f,** hours/week | 3.2E-02 | 3.9E-02 | 3.2E-02 | 4.8E-02 | 1.1E-01 | 2.0E-03 | 2.2E-02 | 6.3E-02 |
| < 1.8 | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. | Ref. |
| ≥ 1.8 - < 5.5 | 0.80 [0.38,1.68] | 0.80 [0.38,1.70] | 0.79 [0.38,1.65] | 0.77 [0.33,1.80] | 0.85 [0.40,1.81] | 0.84 [0.55,1.28] | 0.87 [0.52,1.46] | 0.76 [0.29,1.97] |
| ≥ 5.5 | 0.42 [0.21,0.85] | 0.42 [0.20,0.88] | 0.42 [0.20,0.85] | 0.40 [0.18,0.89] | 0.47 [0.21,1.06] | 0.44 [0.27,0.71] | 0.46 [0.25,0.87] | 0.40 [0.18,0.90] |

All the analyses were stratified by study and adjusted for lymph nodes status, tumour size, tumour grade and (neo)adjuvant systemic treatment. Age of the patients was used as time scale. P-values are considered significant at the Bonferroni corrected threshold of 3.7E-04 for 136 tests. Heterogeneity test by subtype is shown in Supplementary Table S5. Abbreviations: ET: oestrogen therapy; EPT: combined oestrogen and progestin therapy.

a Association estimated in parous women. b More than 6 months before diagnosis. c At diagnosis or within 6 months before diagnosis. d More than 1 year before diagnosis. e At diagnosis or within 1 year before diagnosis. f Categories based on the tertiles of the observed distribution of the variable.

**Table 3. Multivariable Cox regression model on the imputed datasets including all risk factors simultaneously with 10-year all-cause mortality as endpoint.**

|  |  |  |
| --- | --- | --- |
| **Risk factor** | **HR [95% CI]** | **P-value** |
| **Age at menarche** | 1.02 [1.00, 1.04] | 6.8E-02 |
| **Parity** |  |  |
| 0 | Ref. |  |
| 1 | 1.02 [0.91, 1.15] | 7.4E-01 |
| 2 | 0.99 [0.86, 1.15] | 9.0E-01 |
| 3 | 1.01 [0.86, 1.18] | 9.4E-01 |
| 4+ | 1.01 [0.86, 1.18] | 9.2E-01 |
| **Age at first full term pregnancy**, years |  |  |
| < 20 | Ref. |  |
| 20 to < 25 | 0.90 [0.84, 0.96] | 1.9E-03 |
| 25 to < 30 | 0.84 [0.78, 0.90] | 2.8E-06 |
| ≥ 30 | 0.79 [0.72, 0.86] | 2.0E-07 |
| **Time since last full term birth,** years |  |  |
| ≥ 10 | Ref. |  |
| ≥ 5 - < 10 | 1.13 [1.01, 1.28] | 3.2E-02 |
| > 0 - < 5 | 1.31 [1.11, 1.55] | 1.1E-03 |
| ≤ 0 | 1.27 [0.97, 1.66] | 5.9E-02 |
| **Breastfeeding** |  |  |
| Ever vs never | 0.94 [0.82, 1.06] | 2.7E-01 |
| Duration of breastfeeding**,** per 6 months | 1.02 [1.00, 1.04] | 6.9E-02 |
| **BMI,** kg/m2 |  |  |
| 18.5 to < 25 | Ref. |  |
| < 18.5 | 1.31 [0.96, 1.77] | 5.6E-02 |
| 25 to < 30 | 1.04 [0.92, 1.18] | 4.4E-01 |
| ≥ 30 | 1.19 [1.06, 1.34] | 1.1E-03 |
| **Adult height,**  per 5 cm | 0.98 [0.93, 1.03] | 2.8E-01 |
| **Oral contraceptive use** |  |  |
| Ever vs never | 0.91 [0.87, 0.96] | 9.4E-05 |
| **Menopausal hormone therapy** |  |  |
| Never use, postmenopausal | Ref. |  |
| Formera use of ET | 0.75 [0.65, 0.86] | 2.9E-05 |
| Formera use of EPT | 0.85 [0.73, 0.98] | 3.0E-02 |
| Formera use (unknown type) | 0.81 [0.76, 0.86] | 1.1E-11 |
| Currentb use of ET | 0.72 [0.64, 0.82] | 8.3E-07 |
| Currentb use of EPT | 0.61 [0.54, 0.69] | 3.8E-15 |
| Currentb use (unknown type) | 0.78 [0.72, 0.85] | 4.9E-08 |
| Pre/perimenopausal | 0.92 [0.85, 0.99] | 1.7E-02 |
| **Smoking** |  |  |
| Never | Ref. |  |
| Formerc | 1.03 [0.98, 1.07] | 2.3E-01 |
| Currentd | 1.37 [1.27, 1.47] | 0.0E+00 |
| **Alcohol consumptiond**, per 10 g/week | 1.00 [0.99, 1.01] | 6.6E-01 |
| **Cumulative alcohol consumption**, per 10 g/day | 1.00 [0.96, 1.05] | 9.3E-01 |
| **Physical activityd,e**, hours/week |  |  |
| < 1.8 | Ref. |  |
| ≥ 1.8 - < 5.5 | 0.81 [0.39, 1.68] | 5.2E-01 |
| ≥ 5.5 | 0.43 [0.21, 0.86] | 6.3E-03 |

The Cox model was stratified by study and adjusted for lymph nodes status, tumour size, tumour grade, ER status, PR status, HER2 status and (neo)adjuvant systemic treatment. Age of the patients was used as time scale. All the risk factors were simultaneously included in the model.

a More than 6 months before diagnosis. b At diagnosis or within 6 months before diagnosis. c More than 1 year before diagnosis. d At diagnosis or within a year before diagnosis. e Categories based on the tertiles of the observed distribution of the variable. Abbreviations: *ET*: oestrogen therapy; *EPT*: combined oestrogen and progestin therapy.

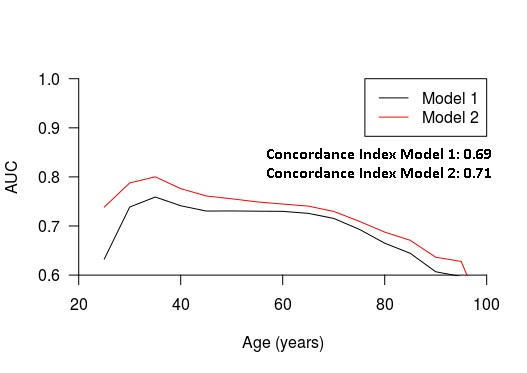


Figure 1. AUC of 10-year all-cause mortality at varying ages, and the concordance index overall for two multivariable models.

Model 1 is stratified by study and includes lymph nodes status, tumour size, tumour grade, ER status, PR status, HER2 status and (neo)adjuvant systemic treatment as covariates. Model 2 additionally includes age at menarche, parity, age at first full term pregnancy, time since last full-term birth, breastfeeding, BMI, adult height, oral contraceptive use, menopausal hormone therapy, smoking, alcohol consumption, cumulative alcohol consumption, and physical activity. The Y-axis represents the AUC. The X-axis represents varying time horizons from diagnosis. Such time horizons are used to define cases (all-cause deaths before or at the time horizon) and controls (event-free patients at the time horizon) and to compute the corresponding AUC. For a given time horizon, the model with the highest AUC has the highest ability to identify patients who experience the event up to that specific time point and patients who are event-free at that specific time point. Since age of the patients is used as time scale, time horizons are in this case age horizons, namely ages at specific time horizons from diagnosis. Hence, at a given age horizon *a*, only patients who died before or at age a and patients who are event-free at age *a*, are included in the computation of the corresponding AUC. The concordance index provides a global assessment of the discriminative power of the models over all ages.