# THE CONTRIBUTION OF RISK FACTORS TO THE HIGHER INCIDENCE OF INVASIVE AND IN SITU BREAST CANCERS AMONG HIGHER EDUCATED WOMEN IN THE EPIC STUDY.

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## Abbreviations

RII: Relative Index of Inequality

HR: Hazard Ratio

BMI: body mass index

HRT: hormonal replacement therapy

EPIC: European Prospective Investigation into Cancer and Nutrition

## Abstract

This paper aims to investigate the role of known risk factors in explaining educational differences in breast cancer incidence. Analyses were based on the European Prospective Investigation into Cancer and Nutrition, and included 242,095 women, 433 *in situ* and 4,469 invasive breast cancers. Reproductive history (age at first full term pregnancy and parity), exposure to endogenous and exogenous hormones, height, and health behaviours were accounted for in the analyses. Relative indices of inequality (RII) for education were estimated using Cox regression models. Higher invasive breast cancer risk was found among women with higher education (RII=1.22: 1.09,1.37). This association was not observed among nulliparous women (RII=1.13: 0.84,1.52). Inequalities in breast cancer incidence decreased substantially after adjusting for reproductive history (RII=1.11: 0.98,1.25), most of the association being explained by age at first full term pregnancy. Each other risk factor explained a small additional part of inequalities in breast cancer incidence. Height contributed most of these factors. When all known risk factors were adjusted for, no association remained between education and invasive breast cancer risk. Inequalities in incidence were more pronounced for *in situ* breast cancers and remained after adjustment for all known risk factors (RII=1.61: 1.07,2.41), especially among nulliparous women.

## Keywords

breast neoplasms; incidence; education; reproductive history; risk factors

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Breast cancer shows a specific pattern with regards to socioeconomic inequalities: higher incidence rates are found among women with higher socioeconomic status [1]. Considering possible risk factors as potential mediators between education and breast cancer incidence helps to better understand the mechanisms of socioeconomic inequalities [2]. Studies generally found that age at first birth and parity (number of full term pregnancies) only in part accounted for the socioeconomic inequalities in breast cancer incidence because of a higher age at first birth and a lower parity among women with higher socioeconomic status [3-7]. Many other risk factors (e.g. hormonal, behavioural or anthropometric) are involved in breast cancer carcinogenesis [8, 9]. As few studies investigated socioeconomic inequalities in breast cancer incidence in relation with risk factors other than age at first birth or parity, it is uncertain how much these other risk factors contribute to socioeconomic inequalities in breast cancer risk [4, 5, 10]. Consequently, it still remains unclear whether a socially stratified distribution of known risk factors totally accounts for the socioeconomic inequalities observed in breast cancer incidence, and which risk factors, in addition to reproductive history, are involved in the mechanisms leading to socioeconomic inequalities in breast cancer incidence.

Based on the natural history of breast cancer, several subgroups of women can be distinguished. Of particular interest are women who never had children, because they have not been exposed to the two main protective risk factors (age at first birth and parity). In addition, it is of interest to distinguish between pre and postmenopausal women, and between women experiencing an invasive cancer and those with an *in situ* breast cancer. Because the risk factors involved [9, 11, 12] and the magnitude of inequalities differ between these groups [5, 7, 10, 13], analyses within these different subgroups may also provide further insights into the causes of socioeconomic inequalities in breast cancer incidence. However, previous studies rarely reported on such stratified analyses.

The European Prospective Investigation into Cancer and Nutrition (EPIC) is a large prospective cohort including several European countries with detailed information on numerous risk factors. Using the EPIC study, we aim to investigate the role of known breast cancer risk factors in explaining educational differences in breast cancer incidence. The large size of the cohort gave us the unique opportunity to perform analyses in several sub-groups and by cancer type (invasive and *in situ)*.

## MATERIALS AND METHODS

### Population

The EPIC cohort is a multi centre prospective cohort conducted in 23 centres in 10 European countries (France, Italy (Florence, Varese, Ragusa, Turin, and Naples), Spain (Asturias, Granada, Murcia, Navarra, and San Sebastian), the UK (Cambridge, Oxford), the Netherlands (Utrecht, Bilthoven), Greece, Germany (Postdam, Heidelberg), Sweden (Malmö, Umea), Denmark (Copenhagen, Aarhus), and Norway) [14, 15]. The study started at the beginning of the 1990s and included about 350,000 women mostly aged between 40-65 years. In most centres subjects were recruited from the general population in a given geographical area (country, region, or city). The French cohort consists of members of the health insurance program for school and university employees, part of the Spanish and Italian centres include blood donors, the Utrecht cohort is based on participants in a mammography screening program, and the cohort in Florence also includes screening program participants. In Oxford, most of the cohort consists of ‘health conscious’ subjects (vegetarian volunteers or healthy eaters). Dietary and lifestyle questionnaires were collected for all subjects at the time of enrolment in the cohort using questionnaires specific to each country.

Women with prevalent cancer at baseline (except non-melanoma skin cancer) were excluded from the cohort (n=19,953). We excluded women with a ratio for energy intake versus energy expenditure in the top and bottom 1% (n=6,796), women with missing information on education (n=14,026), main dietary variables (n=2,441), age at first full term pregnancy or number of full term pregnancies (n=17,785), women who never had menarche (n=1), and women with missing information on date of diagnosis for a cancer prior to the breast cancer (n=3). The date of diagnosis was available for all breast cancer cases. We excluded women from one Swedish centre (Umea) since information on parity and age at first full term pregnancy was missing for most of the women (n=3,592). Compared to other cohorts, the French cohort was a demographically homogeneous population with most women concentrated in the two highest educational levels, leaving little room for studying educational inequalities in this group. Moreover, because of its size, including this cohort would impact the results for the whole EPIC cohort. For these reasons, we decided to exclude the French cohort (n=59,248).

**End points**

Incident cases were identified by population-based cancer registries in Denmark, Italy, the Netherlands, Norway, Spain, Sweden, and the United Kingdom or by active follow-up (Germany, and Greece). For the present analysis, the end of the follow-up period occurred between December 2002 and December 2006. The mean follow-up was 8.4 years. The outcome variable was first primary incident breast cancer. During this follow-up, 4,910 breast cancer cases (invasive n=4,469, *in situ* n=433, uncertain n=8) were reported. Cancer incidence data were coded according to ICD-O-2. Participants who developed a different primary cancer prior to breast cancer were censored at the date of diagnosis of the earlier cancer. Breast cancers with uncertain histology were excluded. We separately analysed invasive and *in situ* breast cancers.

**Statistical analyses**

Analyses were conducted with Cox regression models, stratified on center and age at baseline in 1 year age categories with age as time variable. We computed hazard ratios (HR) using women with primary education or less as reference category. We also computed relative indices of inequality (RII). The calculation of the RII is based on a relative measure of education. Each individual is assigned a fractional rank (from 0 to 1) corresponding to the mean proportion of the population with a *lower* level of education, using the mean rank for ties. For instance, if the lowest educational group comprises 20% of the population, each individual from this group is assigned a value of 0.20/2=0.10. If the next lowest educational group comprises 30% of the population, each individual from this group is assigned a value of 0.20+0.30/2=0.35. The RII is then computed with a Cox regression model using this ranked variable as independent variable and breast cancer as dependent variable. Thus, the RII expresses inequality within the whole socioeconomic continuum. It can be interpreted as the ratio of the expected breast cancer risk between the highest ($100^{th}$ percentile rank) and the lowest ($0^{th}$ percentile rank) educated woman in the study population. Thus, a RII higher than 1 means that breast cancer risk increases with education and is higher among higher educated women. As it takes into account the size and relative position of each educational group, the RII minimizes problems due to differences in distribution of educational degrees across countries participating in the EPIC study. This index is well established and was adapted to compare populations with different educational distributions [16]. This ranked variable was computed by age category, and centre except for the health conscious Oxford cohort, which was a highly selected population. We therefore assigned to these women the rank scores from the Cambridge cohort.

Information about the highest educational level was collected using a questionnaire specific to each country. This allowed taking into account the specificities of each educational system. Each educational classification was then converted into a common classification, which reduces inconsistencies between the different educational systems. Education was categorized in four categories: primary education or less, vocational secondary education, other secondary education, university or vocational post-secondary education. Risk factors were considered as potential intermediate variables that may explain the association observed between education and breast cancer risk. The following variables were included: age at first full term pregnancy (nulliparous, <20, 20-24, 25-29, 30-34, 35-39, 40+), parity (number of full term pregnancies: nulliparous, 1, 2, 3, 4, 5+), age at menarche (<12, 12-14, 15+, missing), ever use of oral contraceptive (yes, no, missing), duration of use of oral contraceptive (never, <=1 year, 2-4, 5-9, 10-14, 15+, missing), ever use of hormonal replacement therapy (HRT) (yes, no, missing), duration of use of HRT (no treatment, <=1 year, 2-4, 5-9, 10+, missing), ever breastfeeding (nulliparous, yes, no, missing), duration of breastfeeding (nulliparous, no breastfeeding, 0-6 months, 6-12, 12+, missing), menopausal status at recruitment (premenopausal, postmenopausal, perimenopausal, surgical postmenopause), age at menopause (post-menopausal with age at menopause <50 years, post-menopausal with age at menopause 50+ years, post-menopausal with age at menopause missing), height (continuous), body mass index (BMI) (<18.5, 18.5-24, 25-29, 30+), alcohol consumption (g/d during 12 months prior to recruitment) (continuous), total physical activity (work and leisure) (inactive, moderately inactive, moderately active, active, missing) [17]. We also coded alcohol consumption as a categorical variable (abstainers and quartiles among drinkers). The results were close to those obtained with alcohol entered as a continuous variable and therefore only the latter was used. When introduced simultaneously, menopausal status and age at menopause were combined into one single categorical variable coded as follows: premenopausal, perimenopausal, surgical postmenopause, postmenopausal with age at menopause <50, postmenopausal with age at menopause 50+, postmenopausal with age at menopause missing. Also, when adjusted for simultaneously, age at first full term pregnancy and number of full term pregnancies were combined into one single categorical variable coded as follows: nulliparous, one pregnancy before 20, one pregnancy between 20 and 24, one pregnancy between 25 and 29, one pregnancy between 30 and 34, one pregnancy between 35 and 39, one pregnancy after 40, two pregnancies and the first before 20, two pregnancies and the first between 20 and 24…

We first adjusted for age at first full term pregnancy and parity (separately and simultaneously). Then we introduced, in addition to the two previous risk factors, each other risk factor separately and successively. We finally considered a model including all risk factors together. We conducted analyses among all women and stratified among nulliparous and parous women, and among premenopausal and postmenopausal women (excluding surgical postmenopausal women). These analyses were conducted separately for invasive and *in situ* breast cancers. Because cancer registration practices, preventive measures, medical services and screening practices differed across EPIC centres, we conducted a heterogeneity analysis by country.

## RESULTS

Most of the 242,095 women belong to the two lowest education groups (Table 1). The distribution across education was similar overall and in parous or postmenopausal women. The level of education was higher among nulliparous and premenopausal women. The distribution across education differed for invasive and *in situ* breast cancers. Comparatively more *in situ* breast cancers occurred among women with college or university education. Women with a lower education showed an older age at menarche, less use of oral contraceptives, a younger age at first full term pregnancy, a higher parity, a greater BMI, a higher level of physical activity, and a lower consumption of alcohol than women with a higher education (Table 2). Age at menopause increased slightly with increasing education.

The relative risk of invasive breast cancer increased as education increased (RII=1.22: 95% CI 1.09, 1.37) (Table 3). Inequalities in breast cancer incidence as measured with the HRs or the RIIs were similar overall and in parous and postmenopausal women. Inequalities were slightly larger among premenopausal women. Among nulliparous women, there was no clear gradient with education: the risk of cancer was nevertheless slightly lower among women with primary education when compared with all other women.

In all women, the association between education and invasive breast cancer was similarly weakened when adjusting for age at first full term pregnancy alone or combined with parity. On the contrary, adjusting for parity alone reduced the estimates by very little. When adjusted for reproductive history (variable combining parity and age at first full term pregnancy), the RII did not reach statistical significance (RII=1.11: 0.98, 1.25) and the HRs remained slightly greater than 1. Similar decreases were found in stratified analyses (parous, pre and postmenopausal women).

Once the largest impact on risks of adjustment for reproductive history was reached, further adjusting for each other risk factor separately did not change or only slightly reduced the HR or the RII (table 4). A substantial larger decrease was nevertheless observed when additionally adjusting for height, although the confidence intervals remained wide. Similar findings were observed in stratified analyses (results not shown).

When all risk factors were adjusted for simultaneously, whether using categorical risks or RII, no association remained between education and invasive breast cancer risk both among all women (RII=0.99: 0.87, 1.12) and in stratified analyses (Table 3).

Inequalities in breast cancer incidence were more pronounced for *in situ* breast cancers (table 5). The HRs were particularly elevated among the highest educated women (university or post-secondary vocational education) when compared with the least educated women (primary education or less) (HR=1.57: 1.18, 2.08). After adjustment for all risk factors, inequalities in breast cancer incidence became statistically nonsignificant among parous women and completely disappeared only among postmenopausal women. In this group, the HR was statistically significantly below unity among women with vocational education when compared with women with primary education or less. Although based on small numbers, the fully adjusted risk estimates remained particularly elevated among nulliparous (RII=4.53: 1.50, 13.7) and premenopausal women (RII=2.72: 1.15, 6.44).

We performed a heterogeneity analysis by country. Heterogeneity was observed for *in situ* breast cancers (p=0.02) but was not reported for invasive breast cancers (p=0.52). More precisely, the estimates in Greek centres differed from the overall estimate both for invasive and *in situ* breast cancers. For *in situ* breast cancers, Spanish, and to a lesser extent German centres, also differed from the overall estimate. In these centres, inequalities in breast cancer incidence were larger than overall.

## DISCUSSION

Highly educated women have a higher breast cancer risk than women with a lower education. We investigated the role of numerous risk factors in explaining educational inequalities in breast cancer incidence. Reproductive history, especially age at first full term pregnancy, partly accounted for these inequalities. Among the other risk factors, height seemed to play a relatively important role. When all breast cancer risk factors were adjusted for, no association remained between education and invasive breast cancer risk whereas substantial inequalities in cancer incidence were still found for *in situ* breast cancers.

### Limitations of the data

The study presents several strengths among which the longitudinal design, the large sample size, and the detailed information on many risk factors. However, some limitations should be addressed. First, we excluded women with missing education information. The risk of breast cancer in this group was similar to that observed among the highest educational group. However, as we do not know how these women are distributed by education, it is not possible to estimate how much the exclusion of these women influenced the estimates. Second, we conducted many simultaneous tests and therefore we cannot rule out that some of the statistically significant effects are due to chance. However, the larger decrease in breast cancer inequalities observed when adjusting for height was also reported in the scarce literature on this issue.

Then, although we adjusted for a large set of risk factors, genetic factors were not accounted for. Genetic mutations in alleles BRCA1 or BRCA2 have been identified as breast cancer risk factors [8]. These mutations could be acquired but are often inherited. Consequently, adjusting for breast cancer history among relatives indirectly accounts for this risk factor. This information was collected in few centres only and was thus not adjusted for in our analyses. However, further analyses restricted to these centres with additional control for family breast cancer history did not suggest an important contribution of this factor to socioeconomic inequalities in breast cancer risk. The population attributable fraction of family history to breast cancer is modest [10, 18]. Thus, the role of this risk factor in socioeconomic inequalities in breast cancer incidence is likely to be small.

Finally, differential attendance to screening was not accounted for but is likely to have induced higher incidence rates among higher educated women. Indeed, routine mammography is more frequently done among higher educated women [19-21]. Educational differences in breast cancer incidence would therefore be further reduced when adjusting for screening. To assess the potential impact of screening on educational differences in breast cancer incidence, we conducted analyses for *in situ* and invasive cancers separately. Also, as screening and case ascertainment practices differ between countries, which may induce differences between countries in socioeconomic inequalities in breast cancer incidence, we conducted heterogeneity analyses. Even though adjusting for screening uptake might reduce educational differences in incidence for all breast cancers, these analyses suggest that this would be more so for *in situ* cancers as discussed below.

We found larger inequalities for *in situ* breast cancers than for invasive breast cancers, as reported elsewhere [13]. Moreover, once adjusted for all risk factors, we still observed substantial educational inequalities for *in situ* breast cancers. The lower statistical power due to small number of *in situ* cases may have contributed to these differential findings. However, differential screening participation rates may also partly account for this finding. *In situ* tumours are indeed more likely than invasive tumours to be detected by routine mammography [12], which is more frequently done in higher educated women. In stratified analyses, inequalities for *in situ* breast cancers were more pronounced among nulliparous and premenopausal women. It is also likely that mammography use is more socially stratified among premenopausal women, as most of them have not yet reached the age-range for mass screening. Opportunistic screening is therefore certainly more frequent in this group than among postmenopausal women and larger socioeconomic inequalities have been found for opportunistic screening than for mass screening [20, 22]. However, the similarity of risk estimates by menopausal status even after adjusting for known risk factors does not support a strong confounding effect of screening. Lower attendance rates to organized screening programs are observed among women living without partner [23-25] and among nulliparous women [25]. As a consequence, in this group too, there might be more opportunistic screening and therefore large inequalities in screening use.

Cases were identified by active follow-up in Greece and Germany. In addition, not all the cancer registries involved in EPIC included screening programs as sources for breast cancer cases [26]. Moreover, educational inequalities in the utilization of mammography screening differed between countries. Inequalities seemed to be smaller in countries with long-sustained countrywide programs (as Sweden or the Netherlands) when compared with countries with recent and/or regional programs (as Italy or Spain) or opportunistic screening (as Greece or

Germany) (Stirbu et al, submitted). Heterogeneity between countries was observed only for *in situ* breast cancers, and the estimates in Greece (for both invasive and *in situ* cancers), Spain, and Germany (for *in situ* cancers) were larger than the overall estimate. These findings may be partly explained by the method used in Greece for case identification. Moreover, these results are consistent with a role of screening in educational inequalities for *in situ* breast cancer incidence, as heterogeneity between countries was limited to these cancers.

Explanations of the key results

Adjusting for reproductive history (age at first full term pregnancy and parity) substantially reduced the association between education and breast cancer risk in our study. The RII decreased by 50% from 1.22 to 1.11, a percentage similar to what is reported in the literature [5, 7]. Age at first full term pregnancy rather than parity was the more relevant factor in explaining socioeconomic inequalities in breast cancer incidence, confirming previous findings [7]. This result may be explained by the stronger association with breast cancer incidence [8] combined with larger educational disparities observed for age at first full term pregnancy than for parity.

One previous study also reported an important contribution of height to inequalities in breast cancer incidence [4]. Height has been shown to be positively associated with the individual's socioeconomic position, such as education, occupational class, workplace success or income [27-29]. This association remains partly unexplained but several factors related to childhood (health, socioeconomic position or diet) are likely to be implied. In addition, the discrimination hypothesis has been suggested: discrimination against short stature would prevent small people to get a high education or a high social position [30]. Height may be associated with breast cancer incidence through several pathways. Height might reflect mammary gland mass, which could be related to breast cancer risk [31]. It is also possible that genetic factors and environmental factors in childhood such as diet or physical activity may affect both attained height and hormonal factors (especially growth hormones), the latter leading to an increased risk of breast cancer [29, 32]. In addition, height might also be a marker of the socioeconomic position, including aspects that are not accounted for by education, and thus a marker of other breast cancer risk factors. Further studies are needed to explore the role of specific factors indicated by height in explaining socioeconomic inequalities in breast cancer incidence.

Controversial results are reported in the literature with regards to the level of socioeconomic inequalities in breast cancer incidence by menopausal status, with a steeper increase in breast cancer risk by educational level reported after menopause [5] or before menopause [10] as in our study. When interpreting these results, it is particularly difficult to disentangle the effect of menopause from the effect of birth cohort. The differences in inequalities in breast cancer incidence between pre- and postmenopausal women may actually be partly explained by factors that differ by birth cohort, such as age at first full term pregnancy [33]. Our results do support this hypothesis: the RIIs by menopausal status were quite similar once educational differences in age at first full term pregnancy were accounted for.

We used education as a measure of the socioeconomic position. Education is a suitable measure when investigating socioeconomic inequalities in health among women as this information is available for all women, including older women or housewives [34]. Also, education is quite easily and accurately recorded and it is unaffected by poor health in adulthood. Higher education may be associated with health through different pathways – subjects with higher education may be more receptive to prevention messages and may have a better ability to change their health behaviour and to better use the health care system [34, 35]. A similar association between the socioeconomic position and breast cancer risk is also reported using other indicators. The more commonly used are income or occupational class, which measure different dimensions of the socioeconomic position [1, 36, 37]. Future studies are needed to assess whether similar patterns are observed when using such other indicators of the socioeconomic position, and especially those that capture more material dimensions of the socioeconomic position, such as income and wealth.

Contrary to most other cancer sites, breast cancer incidence shows a specific pattern with higher incidence rates among women with high socioeconomic position. This exceptional association calls for understanding. This study documented the relevant factors that explain this association with more precision and detail than any previous study. Age at first full term pregnancy, parity and height were the three main factors that accounted for nearly all educational differences in breast cancer incidence. In addition, this study was among the first to document that these inequalities were particularly pronounced for *in situ* breast cancer incidence. These inequalities could not be fully explained by known risk factors. We believe that a differential earlier detection bias may explain this result.

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Table 1: Characteristics of Women from the EPIC Study by Education.

| | All | Education | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|
| | | Primary | | Vocational secondary | | Other secondary | | University or post-secondary vocational | |
| | N | N | % | N | % | N | % | N | % |
| All women | 242,095 | 83,303 | 34 | 68,872 | 29 | 41,905 | 17 | 48,015 | 20 |
| Invasive breast cancers | 4,469 | 1,523 | 34 | 1,381 | 31 | 727 | 16 | 838 | 19 |
| *In situ* breast cancers | 433 | 139 | 32 | 107 | 25 | 70 | 16 | 117 | 27 |
| Parous women | 201,668 | 76,103 | 38 | 58,808 | 29 | 33,414 | 17 | 33,343 | 16 |
| Invasive breast cancers | 3,805 | 1,356 | 36 | 1,186 | 31 | 613 | 16 | 650 | 17 |
| *In situ* breast cancers | 370 | 128 | 35 | 95 | 26 | 61 | 16 | 86 | 23 |
| Nulliparous women | 40,427 | 7,200 | 18 | 10,064 | 25 | 8,491 | 21 | 14,672 | 36 |
| Invasive breast cancers | 664 | 167 | 25 | 195 | 30 | 114 | 17 | 188 | 28 |
| *In situ* breast cancers | 63 | 11 | 18 | 12 | 19 | 9 | 14 | 31 | 49 |
| Premenopausal women[a] | 90,244 | 21,060 | 23 | 24,157 | 27 | 19,191 | 21 | 25,836 | 29 |
| Invasive breast cancers | 1,067 | 276 | 26 | 272 | 25 | 230 | 22 | 289 | 27 |
| *In situ* breast cancers | 110 | 23 | 21 | 27 | 25 | 20 | 18 | 40 | 36 |
| Postmenopausal women[a] | 102,721 | 43,319 | 45 | 28,959 | 28 | 13,852 | 14 | 13,591 | 13 |
| Invasive breast cancers | 2,389 | 947 | 40 | 756 | 32 | 323 | 13 | 363 | 15 |
| *In situ* breast cancers | 230 | 93 | 40 | 54 | 23 | 38 | 17 | 45 | 20 |

[a] Some women are perimenopaused or have surgical menopause.

Table 2: Distribution of Breast Cancer Risk Factors Among all Women and by Education Among EPIC Women.

| | All women | | | Education | | | |
|---|---|---|---|---|---|---|---|
| | | | | Primary | Vocational secondary | Other secondary | University or post-secondary vocational |
| | **Mean (±SD)** | | | **Mean (±SD)** | **Mean (±SD)** | **Mean (±SD)** | **Mean (±SD)** |
| Age at recruitment | 50.3 (±10.2) | | | 54.1 (±8.9) | 50.2 (±9.5) | 47.7 (±10.2) | 46.2 (±10.7) |
| Number of full term pregnancies | 2.3 (±1.0) | | | 2.5 (±1.2) | 2.2 (±0.9) | 2.2 (±1.0) | 2.1 (±0.9) |
| Age at first full term pregnancy | 24.8 (±4.4) | | | 23.7 (±4.2) | 24.3 (±4.2) | 25.7 (±4.2) | 27.3 (±4.6) |
| Age at menopause[a] | 48.7 (±4.7) | | | 48.6 (±4.8) | 48.8 (±4.7) | 48.8 (±4.7) | 49.0 (±4.6) |
| Height (cm) | 162.5 (±7.0) | | | 159.1 (±6.8) | 164.0 (±6.2) | 164.1 (±6.6) | 164.5 (±6.4) |
| | **Median (IQ range)** | | | **Median (IQ range)** | **Median (IQ range)** | **Median (IQ range)** | **Median (IQ range)** |
| Alcohol consumption in g/day | 3.2 (10.1) | | | 1.4 (7.4) | 4.1 (9.9) | 3.7 (10.2) | 6.2 (11.5) |
| | **$N_I$** | **$N_{IS}$** | **%** | **%** | **%** | **%** | **%** |
| Duration of breast feeding | | | | | | | |
| *Nulliparous* | 664 | 63 | 16.7 | 8.6 | 14.6 | 20.2 | 30.6 |
| *Parous : Never breastfed* | 460 | 53 | 9.7 | 11.2 | 10.8 | 8.8 | 6.1 |
| *Parous : 0-6 months* | 1376 | 135 | 28.4 | 30.0 | 32.4 | 24.6 | 23.1 |
| *Parous : 6-12 months* | 836 | 93 | 18.7 | 21.0 | 19.0 | 17.6 | 15.6 |
| *Parous : >12 months* | 957 | 72 | 22.9 | 26.5 | 18.7 | 24.0 | 21.7 |
| *Parous : Missing information* | 176 | 17 | 3.6 | 2.7 | 4.5 | 4.8 | 2.9 |
| Age at menarche | | | | | | | |
| *<12* | 577 | 67 | 14.1 | 13.9 | 12.6 | 15.3 | 15.9 |
| *12-14* | 3032 | 294 | 67.8 | 65.7 | 67.5 | 69.6 | 70.0 |
| *>14* | 788 | 63 | 16.9 | 19.4 | 18.3 | 14.0 | 13.2 |
| *Missing* | 72 | 9 | 1.2 | 1.1 | 1.6 | 1.1 | 0.9 |
| Duration of use of oral contraceptive | | | | | | | |
| *Never* | 1928 | 188 | 41.4 | 60.6 | 31.7 | 34.6 | 28.0 |
| *1 year or less* | 473 | 42 | 11.0 | 10.6 | 10.4 | 12.5 | 11.2 |
| *2-4 years* | 567 | 49 | 13.2 | 9.4 | 14.2 | 15.4 | 16.3 |
| *5-9 years* | 501 | 48 | 12.2 | 7.2 | 14.1 | 13.4 | 17.0 |
| *10-14 years* | 381 | 44 | 8.6 | 5.1 | 11.1 | 8.6 | 11.3 |
| *15+ years* | 403 | 40 | 7.7 | 4.7 | 11.1 | 6.3 | 9.0 |
| *Missing* | 216 | 22 | 5.9 | 2.4 | 7.4 | 9.2 | 7.2 |
| Duration of use of hormonal replacement therapy | | | | | | | |
| *No treatment* | 2615 | 257 | 70.7 | 72.9 | 63.2 | 76.4 | 72.9 |
| *1 year or less* | 361 | 36 | 6.8 | 7.3 | 7.5 | 6.0 | 5.4 |
| *2-4 years* | 408 | 40 | 6.6 | 5.5 | 8.6 | 6.3 | 5.9 |
| *5-9 years* | 357 | 26 | 4.4 | 3.7 | 6.2 | 3.6 | 3.7 |
| *10+ years* | 225 | 18 | 2.4 | 2.4 | 3.5 | 1.7 | 1.5 |
| *Missing* | 503 | 56 | 9.1 | 8.2 | 11.1 | 5.9 | 10.6 |
| BMI ($kg/m^2$) | | | | | | | |
| *<18.5* | 47 | 4 | 1.5 | 0.7 | 1.5 | 1.9 | 2.5 |
| *18.5-24* | 2261 | 227 | 51.6 | 33.9 | 55.9 | 61.7 | 67.3 |
| *25-29* | 1501 | 143 | 31.9 | 39.7 | 31.1 | 27.6 | 23.4 |
| *30+* | 660 | 59 | 15.0 | 25.7 | 11.5 | 8.8 | 6.8 |
| Total physical activity | | | | | | | |
| *Inactive* | 612 | 58 | 11.4 | 4.0 | 13.9 | 12.2 | 20.1 |
| *Moderately inactive* | 1071 | 102 | 21.6 | 17.4 | 22.1 | 20.3 | 29.5 |
| *Moderately active* | 1826 | 200 | 41.6 | 57.4 | 34.0 | 33.6 | 31.9 |
| *Active* | 444 | 66 | 9.7 | 10.9 | 10.2 | 7.9 | 8.3 |
| *Missing* | 516 | 7 | 15.7 | 10.3 | 19.8 | 26.0 | 10.2 |

BMI body mass index; IQ range inter-quartile range; $N_I$=number of invasive breast cancers; $N_{IS}$=number of *in situ* breast cancers SD standard deviation; [a] Among postmenopausal women

Table 3: Invasive Breast Cancers: Hazard Ratios and Relative Indices of Inequality by Education Among all Women and Among Nulliparous, Parous, Premenopausal and Postmenopausal EPIC Women After Adjustment for Reproductive History and all Risk Factors Together.

| | | | Primary | Vocational secondary | | Other secondary | | University or post-seconday vocational | |
|---|---|---|---|---|---|---|---|---|---|
| Model adjusted for | RII | 95% CI | HR | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| All women | | | | | | | | | |
| Model 0: Stratified for age and center[a] | 1.22 | 1.09, 1.37 | 1 | 1.09 | 1.01, 1.18 | 1.12 | 1.02, 1.23 | 1.19 | 1.08, 1.31 |
| M0 + Parity | 1.18 | 1.05, 1.33 | 1 | 1.08 | 0.99, 1.17 | 1.10 | 1.00, 1.21 | 1.16 | 1.06, 1.27 |
| M0 + Age at first full term pregnancy | 1.10 | 0.98, 1.24 | 1 | 1.06 | 0.98, 1.15 | 1.07 | 0.97, 1.17 | 1.10 | 1.00, 1.21* |
| M0 + Reproductive history[b] | 1.11 | 0.98, 1.25 | 1 | 1.06 | 0.98, 1.15 | 1.07 | 0.97, 1.18 | 1.10 | 1.00, 1.21 |
| M0 + All risk factors[c] | 0.99 | 0.87, 1.12 | 1 | 1.01 | 0.93, 1.10 | 1.00 | 0.91, 1.11 | 1.01 | 0.91, 1.12 |
| Nulliparous women | | | | | | | | | |
| Model 0: Stratified for age and center[a] | 1.13 | 0.84, 1.52 | 1 | 1.15 | 0.92, 1.44 | 1.10 | 0.85, 1.42 | 1.10 | 0.86, 1.38 |
| M0 + All risk factors[d] | 1.00 | 0.73, 1.37 | 1 | 1.10 | 0.87, 1.38 | 1.02 | 0.78, 1.33 | 1.00 | 0.78, 1.27 |
| Parous women | | | | | | | | | |
| Model 0: Stratified for age and center[a] | 1.22 | 1.07, 1.38 | 1 | 1.08 | 0.99, 1.18 | 1.12 | 1.01, 1.24 | 1.20 | 1.08, 1.33 |
| M0 + Parity | 1.20 | 1.06, 1.36 | 1 | 1.07 | 0.98, 1.17 | 1.11 | 1.00, 1.13 | 1.19 | 1.07, 1.32 |
| M0 + Age at first full term pregnancy | 1.11 | 0.97, 1.26 | 1 | 1.06 | 0.97, 1.15 | 1.07 | 0.96, 1.19 | 1.11 | 1.00, 1.24* |
| M0 + Reproductive history | 1.11 | 0.98, 1.27 | 1 | 1.06 | 0.97, 1.15 | 1.07 | 0.97, 1.19 | 1.12 | 1.01, 1.25 |
| M0 + All risk factors[c] | 0.99 | 0.87, 1.14 | 1 | 1.01 | 0.92, 1.10 | 1.01 | 0.91, 1.12 | 1.03 | 0.92, 1.15 |
| Premenopausal women | | | | | | | | | |
| Model 0: Stratified for age and center[a] | 1.33 | 1.04, 1.69 | 1 | 1.09 | 0.90, 1.33 | 1.22 | 1.01, 1.49 | 1.24 | 1.02, 1.51 |
| M0 + Parity | 1.30 | 1.02, 1.66 | 1 | 1.08 | 0.89, 1.31 | 1.21 | 0.99, 1.47 | 1.22 | 1.00, 1.48 |
| M0 + Age at first full term pregnancy | 1.11 | 0.86, 1.44 | 1 | 1.04 | 0.86, 1.27 | 1.13 | 0.92, 1.38 | 1.09 | 0.89, 1.34 |
| M0 + Reproductive history | 1.14 | 0.88, 1.47 | 1 | 1.05 | 0.86, 1.28 | 1.14 | 0.93, 1.39 | 1.11 | 0.91, 1.36 |
| M0 + All risk factors[e] | 1.00 | 0.77, 1.30 | 1 | 1.01 | 0.83, 1.23 | 1.06 | 0.87, 1.30 | 1.01 | 0.81, 1.24 |
| Postmenopausal women | | | | | | | | | |
| Model 0: Stratified for age and center[a] | 1.21 | 1.03, 1.41 | 1 | 1.09 | 0.98, 1.20 | 1.08 | 0.94, 1.23 | 1.20 | 1.05, 1.37 |
| M0 + Parity | 1.17 | 1.00*, 1.37 | 1 | 1.07 | 0.97, 1.19 | 1.06 | 0.93, 1.21 | 1.17 | 1.02, 1.33 |
| M0 + Age at first full term pregnancy | 1.09 | 0.93, 1.29 | 1 | 1.05 | 0.95, 1.17 | 1.02 | 0.89, 1.17 | 1.11 | 0.97, 1.27 |
| M0 + Reproductive history | 1.10 | 0.93, 1.29 | 1 | 1.05 | 0.95, 1.17 | 1.02 | 0.89, 1.17 | 1.11 | 0.97, 1.27 |
| M0 + All risk factors[f] | 0.95 | 0.80, 1.12 | 1 | 0.99 | 0.89, 1.10 | 0.94 | 0.82, 1.08 | 1.00 | 0.87, 1.15 |

CI confidence interval; HR hazard ratios; RII relative index of inequality; *: 1 included in the CI; [a] Model 0 controls for age at baseline (1-year age category) and center; [b] Reproductive history: variable combining parity and age at first full term pregnancy; [c] reproductive history, ever breast feeding, common risk factors [g], ever use of hormonal replacement therapy, menopausal status&age at menopause combined; [d] common risk factors [g], ever use of hormonal replacement therapy, menopausal status&age at menopause combined; [e] reproductive history, ever breast feeding, common risk factors [g]; [f] reproductive history, ever breast feeding, common risk factors [g], ever use of hormonal replacement therapy, age at menopause; [g] Common risk factors: age at menarche, ever use of oral contraceptives, height, BMI, alcohol consumption, total physical activity.

Table 4: Invasive Breast Cancers: Hazard Ratios and Relative Indices of Inequality by Education Among all EPIC Women Adjusted for Each Risk Factor Separately.

| Education | Primary | Vocational secondary | | Other secondary | | University or post-secondary vocational | | | |
|---|---|---|---|---|---|---|---|---|---|
| Model adjusted for | HR | HR | 95% CI | HR | 95% CI | HR | 95% CI | RII | 95% CI |
| Model 0: Stratified for age and center [a] | 1 | 1.09 | 1.01, 1.18 | 1.12 | 1.02, 1.23 | 1.19 | 1.08, 1.31 | 1.22 | 1.09, 1.37 |
| Model 1: Model 0 + reproductive history[b] | 1 | 1.06 | 0.98, 1.15 | 1.07 | 0.97, 1.18 | 1.10 | 1.00, 1.21 | 1.11 | 0.98, 1.25 |
| Model 1 + age at menarche | 1 | 1.06 | 0.98, 1.15 | 1.07 | 0.97, 1.17 | 1.10 | 1.00, 1.21* | 1.10 | 0.98, 1.24 |
| Model 1 + ever breastfeeding | 1 | 1.06 | 0.98, 1.15 | 1.07 | 0.97, 1.18 | 1.10 | 1.00, 1.22 | 1.11 | 0.98, 1.25 |
| Model 1 + duration of breastfeading | 1 | 1.06 | 0.98, 1.15 | 1.07 | 0.97, 1.18 | 1.10 | 1.00, 1.21* | 1.10 | 0.98, 1.25 |
| Model 1 + ever use of HRT | 1 | 1.05 | 0.97, 1.14 | 1.06 | 0.96, 1.16 | 1.09 | 0.99, 1.20 | 1.09 | 0.97, 1.23 |
| Model 1 + ever use of oral contraceptive | 1 | 1.06 | 0.98, 1.15 | 1.06 | 0.97, 1.17 | 1.09 | 0.99, 1.21 | 1.10 | 0.97, 1.24 |
| Model 1 + duration of use of oral contraceptive | 1 | 1.06 | 0.98, 1.15 | 1.06 | 0.96, 1.17 | 1.09 | 0.99, 1.21 | 1.09 | 0.97, 1.23 |
| Model 1 + duration of use of HRT | 1 | 1.05 | 0.97, 1.14 | 1.06 | 0.96, 1.16 | 1.09 | 0.99, 1.20 | 1.09 | 0.97, 1.23 |
| Model 1 + alcohol consumption | 1 | 1.06 | 0.97, 1.15 | 1.06 | 0.96, 1.16 | 1.08 | 0.98, 1.19 | 1.08 | 0.96, 1.22 |
| Model 1 + menopausal status | 1 | 1.06 | 0.98, 1.15 | 1.07 | 0.97, 1.18 | 1.10 | 1.00, 1.21* | 1.10 | 0.98, 1.24 |
| Model 1 + age at menopause | 1 | 1.06 | 0.97, 1.15 | 1.06 | 0.96, 1.17 | 1.09 | 0.99, 1.20 | 1.09 | 0.97, 1.23 |
| Model 1 + height | 1 | 1.04 | 0.96, 1.13 | 1.04 | 0.94, 1.14 | 1.06 | 0.96, 1.17 | 1.05 | 0.93, 1.18 |
| Model 1 + BMI | 1 | 1.07 | 0.98, 1.16 | 1.07 | 0.98, 1.18 | 1.11 | 1.01, 1.22 | 1.11 | 0.99, 1.26 |
| Model 1 + total physical activity | 1 | 1.05 | 0.97, 1.14 | 1.05 | 0.96, 1.16 | 1.08 | 0.98, 1.19 | 1.08 | 0.95, 1.22 |
| Model adjusted for all risk factors[c] | 1 | 1.01 | 0.93, 1.10 | 1.00 | 0.91, 1.11 | 1.01 | 0.91, 1.12 | 0.99 | 0.87, 1.12 |

BMI body mass index; CI confidence interval; HR hazard ratio; HRT hormonal replacement therapy; RII relative index of inequality; *: 1 included in the CI; [a] Model 0 controls for age at baseline (1-year age category) and center; [b] Reproductive history: variable combining parity and age at first full term pregnancy; [c] reproductive history, ever breast feeding, age at menarche, ever use of HRT and oral contraceptives, alcohol consumption, menopausal status&age at menopause combined, height, BMI, total physical activity

Table 5: *In situ* Breast Cancers: Hazard Ratios and Relative Indices of Inequality by Education Among all Women and Among Nulliparous, Parous, Premenopausal and Postmenopausal EPIC Women After Adjustment for Reproductive History and all Risk Factors Together.

| | | | Primary | Vocational secondary | | Other secondary | | University or post-secondary vocational | |
|---|---|---|---|---|---|---|---|---|---|
| Model adjusted for | RII | 95% CI | HR | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| All women | | | | | | | | | |
| Model 0: Stratified for age and center [a] | 1.86 | 1.28, 2.70 | 1 | 0.94 | 0.71, 1.24 | 1.24 | 0.91, 1.70 | 1.57 | 1.18, 2.08 |
| Model 0 + Reproductive history[b] | 1.70 | 1.15, 2.51 | 1 | 0.92 | 0.69, 1.21 | 1.20 | 0.87, 1.65 | 1.47 | 1.10, 1.97 |
| Model 0 + All risk factors[c] | 1.61 | 1.07, 2.41 | 1 | 0.89 | 0.67, 1.18 | 1.15 | 0.83, 1.59 | 1.40 | 1.03, 1.90 |
| Nulliparous women | | | | | | | | | |
| Model 0: Stratified for age and center [a] | 3.92 | 1.38, 11.1 | 1 | 1.46 | 0.48, 2.78 | 1.39 | 0.53, 3.63 | 2.55 | 1.17, 5.55 |
| Model 0 + All risk factors[d] | 4.53 | 1.50, 13.7 | 1 | 1.08 | 0.44, 2.64 | 1.45 | 0.54, 3.86 | 2.68 | 1.18, 6.08 |
| Parous women | | | | | | | | | |
| Model 0: Stratified for age and center [a] | 1.68 | 1.11, 2.53 | 1 | 0.93 | 0.69, 1.24 | 1.28 | 0.92, 1.79 | 1.44 | 1.05, 1.97 |
| Model 0 + Reproductive history | 1.52 | 0.99, 2.32 | 1 | 0.90 | 0.67, 1.22 | 1.23 | 0.87, 1.72 | 1.33 | 0.96, 1.84 |
| Model 0 + All risk factors[c] | 1.39 | 0.89, 2.17 | 1 | 0.87 | 0.64, 1.17 | 1.16 | 0.82, 1.64 | 1.25 | 0.89, 1.75 |
| Premenopausal women | | | | | | | | | |
| Model 0: Stratified for age and center [a] | 2.98 | 1.37, 6.47 | 1 | 1.97 | 1.03, 3.78 | 1.89 | 0.96, 3.71 | 2.70 | 1.46, 4.98 |
| Model 0 + Reproductive history | 2.92 | 1.28, 6.68 | 1 | 1.98 | 1.02, 3.81 | 1.92 | 0.97, 3.82 | 2.68 | 1.41, 5.10 |
| Model 0 + All risk factors[e] | 2.68 | 1.13, 6.34 | 1 | 1.90 | 0.97, 3.71 | 1.90 | 0.94, 3.83 | 2.51 | 1.28, 4.93 |
| Postmenopausal women | | | | | | | | | |
| Model 0: Stratified for age and center [a] | 1.26 | 0.76, 2.10 | 1 | 0.70 | 0.49, 1.00 | 1.14 | 0.76, 1.71 | 1.16 | 0.78, 1.71 |
| Model 0 + Reproductive history | 1.09 | 0.65, 1.84 | 1 | 0.67 | 0.47, 0.96 | 1.05 | 0.70, 1.59 | 1.03 | 0.69, 1.55 |
| Model 0 + All risk factors[f] | 0.94 | 0.55, 1.64 | 1 | 0.62 | 0.43, 0.90 | 0.96 | 0.63, 1.46 | 0.93 | 0.61, 1.42 |

CI confidence interval; HR hazard ratio; RII relative index of inequality; [a] Model 0 controls for age at baseline (1-year age category) and center; [b] Reproductive history: variable combining parity and age at first full term pregnancy; [c] reproductive history, ever breast feeding, common risk factors [g], ever use of hormonal replacement therapy, menopausal status&age at menopause combined; [d] common risk factors [g], ever use of hormonal replacement therapy, menopausal status&age at menopause combined; [e] reproductive history, ever breast feeding, common risk factors [g]; [f] reproductive history, ever breast feeding, common risk factors [g], ever use of hormonal replacement therapy, age at menopause; [g] Common risk factors: age at menarche, ever use of oral contraceptives, height, BMI, alcohol consumption, total physical activity.

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