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Investigating The Effects of The Model Covariates on Breast Cancer Risk Using the Knapp-Hartung Adjusted Random-Effects Meta-Regression

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Abstract- Background: ***Breast cancer is a leading cause of cancer-related morbidity and mortality among women worldwide. Reproductive and familial factors are known to influence breast cancer risk, but their effects vary across studies. This study aimed to investigate the impact of selected covariates on breast cancer risk using a Knapp–Hartung adjusted random-effects meta-regression.***

Methods: ***A random-effects meta-regression analysis was conducted using data from 60 samples. The model assessed the associations between breast cancer risk and age at menarche, history of breastfeeding, age at menopause, and family history of cancer. The Knapp–Hartung adjustment was applied to account for uncertainty in between-study variance. All statistical analyses were performed using R software.***

Results: ***Ever breastfed was significantly associated with a reduced risk of breast cancer (coefficient = −0.4135, p = 0.001), Menopause (coefficient = 0.1082, p = 0.024) and family history of cancer (coefficient = 0.2435, p = 0.015) were significantly associated with increased breast cancer risk. Menarche demonstrated a positive but borderline significant association with breast cancer risk (coefficient = 0.1116, p = 0.063).***

Conclusion: ***Breastfeeding appears to confer a protective effect against breast cancer, whereas menopause and family history of cancer are associated with elevated risk. These findings emphasize the importance of reproductive and familial factors in breast cancer risk evaluation and prevention strategies.***

Keywords: ***Breast Cancer, Meta-Regression, Knapp–Hartung Adjustment, Ever Breastfed Menopause, Menarche, Family History of Breast Cancer***

I. INTRODUCTION

Knapp–Hartung adjusted random-effects meta-regression is a robust statistical approach used to examine the influence of study-level covariates on effect estimates while appropriately accounting for between-study heterogeneity (Knapp & Hartung, 2003). By incorporating uncertainty in the estimation of between-study variance, this method provides more conservative and reliable statistical inference, particularly when heterogeneity is present across studies (IntHout et al., 2014).

This analytical framework is especially suitable for investigating breast cancer risk factors, as evidence from epidemiological studies often shows substantial variability due to differences in populations, study designs, and measurement methods (Collaborative Group on Hormonal Factors in Breast Cancer, 2012). Meta-regression extends traditional meta-analysis by allowing the assessment of multiple covariates as potential sources of heterogeneity, thereby facilitating a deeper understanding of how reproductive and familial characteristics influence breast cancer risk (Higgins & Thompson, 2004). Breast cancer remains one of the most prevalent cancers among women worldwide, with reproductive factors such as age at menarche, breastfeeding history, and age at menopause, as well as genetic predisposition reflected by family history of cancer, consistently identified as important determinants of risk (Colditz et al., 2006; Collaborative Group on Hormonal Factors in Breast Cancer, 2012). However, inconsistent findings across individual studies highlight the need for a rigorous synthesis method that can evaluate these covariates simultaneously while controlling for heterogeneity.

Reproductive factors have consistently been associated with breast cancer risk. Earlier age at

menarche and later age at menopause are linked to prolonged lifetime exposure to endogenous hormones, which is thought to increase breast cancer susceptibility (Collaborative Group on Hormonal Factors in Breast Cancer, 2012). Breastfeeding, on the other hand, has been shown to have a protective effect, potentially through hormonal mechanisms that reduce ovulatory cycles and breast tissue proliferation (Victora et al., 2016). Additionally, family history of cancer, particularly breast cancer in first-degree relatives, is a well-established non-modifiable risk factor reflecting genetic predisposition and shared environmental influences (Colditz et al., 2006). While individual studies provide important insights, inconsistencies across studies highlight the need for a rigorous synthesis method that accounts for heterogeneity and evaluates covariates simultaneously.

Therefore, this study employed a Knapp–Hartung adjusted random-effects meta-regression to investigate the effects of age at menarche, breastfeeding history, age at menopause, and family history of cancer on breast cancer risk. This approach aims to generate more reliable estimates of covariate effects and contribute to a clearer understanding of key risk factors relevant to breast cancer prevention and risk assessment.

1.1 Statement of Problem

Breast cancer is the most common cancer among women worldwide and a leading cause of cancer-related morbidity and mortality. Epidemiological studies have identified reproductive factors such as age at menarche, age at menopause, and breastfeeding history as well as genetic predisposition, reflected by family history of cancer, as important determinants of breast cancer risk (Collaborative Group on Hormonal Factors in Breast Cancer, 2012; Victora et al., 2016). However, findings across individual studies have been inconsistent, with reported effect sizes varying substantially due to differences in study populations, designs, and measurement methods.

This variability, or between-study heterogeneity, complicates the accurate estimation of the influence of these risk factors. Conventional meta-analytic techniques may inadequately address such heterogeneity, potentially leading to misleading conclusions. Moreover, standard random-effects meta-regression methods can underestimate the uncertainty in between-study variance, resulting in overly narrow confidence intervals and inflated significance levels when synthesizing results across heterogeneous studies (Knapp & Hartung, 2003; IntHout et al., 2014).

Although advanced methods such as Knapp–Hartung adjusted random-effects meta-regression provide more reliable inference by accounting for uncertainty in heterogeneity, few studies have applied this approach to simultaneously evaluate multiple reproductive and familial covariates in relation to breast cancer risk. Therefore, there is a need for a rigorous synthesis of existing evidence to clarify the magnitude and direction of these associations and to generate robust estimates of covariate effects.

1.1.1 Aim and Objectives.

This study aims to investigate the effects of the model covariates on breast cancer risk using the Knapp-Hartung adjusted random-effects meta-regression.

II. LITERATURE REVIEW

Breast cancer is a leading cause of cancer related Disease burden and Death burden among women, with risk influenced by hormonal, reproductive, genetic, and environmental determinants (Collaborative Group on Hormonal Factors in Breast Cancer, 2012). Epidemiological research has consistently shown that reproductive life-course events, such as menarche, menopause, ever breastfed and family history of breast cancer substantially affect breast cancer risk, likely through hormonal mechanisms involving prolonged exposure to endogenous estrogens and progesterone (Collaborative Group on Hormonal Factors in Breast Cancer, 2012).

Menarche which is the age at which menstruation begins, is a well-established reproductive factor associated with breast cancer risk. Younger age at menarche is linked to longer lifetime exposure to estrogen, which enhances breast tissue proliferation and susceptibility to malignant transformation. A large individual participant meta-analysis revealed that breast cancer risk increases by approximately 5% for

each year younger at menarche (Collaborative Group on Hormonal Factors in Breast Cancer, 2012). Systematic reviews also suggest that later age at menarche is protective across breast cancer subtypes, particularly hormone receptor–positive tumors (Cancer Research UK, 2020). Breastfeeding is another reproductive factor consistently associated with reduced breast cancer risk. Biological mechanisms include reduced ovulatory cycles due to lactation and increased differentiation and shedding of breast epithelial cells, which may decrease the accumulation of genetic damage (NCBI Bookshelf, 2012). Meta-analytic evidence confirms that breastfeeding lowers breast cancer risk, and the protective effect tends to be stronger with longer duration of breastfeeding (NCBI Bookshelf, 2012). The protective influence of breastfeeding has been observed in diverse populations and across hormone receptor subtypes, reinforcing its importance from both biological and public health perspectives (Goswami et al., 2023). Menopause also increases breast cancer risk by prolonging the duration of endogenous hormone exposure. Several studies indicate that each additional year of delayed menopause increases risk, consistent with the cumulative hormonal exposure hypothesis (NCBI Bookshelf, 2012). This pattern holds across multiple epidemiological reports, with later menopause showing stronger associations for hormone receptor–positive breast cancers in some subgroup analyses (NCBI Bookshelf, 2012). Family history of breast cancer remains one of the most robust non-modifiable risk factors. Women with first-degree relatives affected by breast cancer have significantly elevated risk compared with those without a family history, reflecting both genetic susceptibility and shared environmental influences (Goswami et al., 2023; Indian Journal of Cancer, 2023). Genetic predisposition interacts with reproductive exposures in complex ways, modifying the relative influence of factors such as age at menarche, age at menopause, and breastfeeding history in different populations (European Journal of Medical Research, 2022).

Despite the general consistency in the direction of associations between reproductive factors and breast cancer, effect sizes vary across studies, often due to differences in populations, study designs, measurement methods, and other contextual factors. Meta-analyses focusing on specific populations, such as Indian or Iranian women, have reported varying magnitudes of associations for factors including age at menarche and breastfeeding (PubMed, 2019). This between-study heterogeneity highlights the limitations of traditional meta-analysis when it does not account for covariate effects. Meta-regression extends conventional meta-analysis by including study-level covariates to explain sources of variability in effect estimates across studies and to better interpret contextual differences (Wikipedia, 2025).

While random-effects meta-regression allows the inclusion of covariates to explain between-study heterogeneity, standard inference procedures can underestimate uncertainty in the estimated between-study variance, especially when the number of studies is limited or their sizes vary considerably. The Knapp–Hartung adjustment refines standard random-effects methods by using a Student's t distribution for inference and adjusting variance estimates, producing more conservative and reliable confidence intervals and hypothesis tests (Jackson, Law, & Rücker, 2017). Methodological studies demonstrate that the Hartung–Knapp-Sidik-Jonkman approach yields error rates closer to nominal levels than conventional random-effects methods and can reduce the number of statistically significant results, reflecting improved control of false positives (IntHout, Ioannidis, & Borm, 2014).

Despite the wealth of research on individual reproductive risk factors, relatively few studies have applied advanced meta-regression methods with Knapp–Hartung adjustment to simultaneously evaluate multiple covariates. Incorporating this approach allows researchers to improve the robustness of estimates and clarify relationships that might otherwise be obscured by simplistic models. Such refined analysis is critical for developing evidence-based strategies for breast cancer prevention, risk prediction, and targeted interventions in high-risk populations (Jackson, Law, & Rücker, 2017; IntHout, Ioannidis, & Borm, 2014).

2.1 Literature Gap

Despite extensive research on reproductive and familial risk factors for breast cancer, inconsistencies persist in the reported effect sizes of factors such as menarche, menopause, ever breastfed, and family

history of breast cancer (Collaborative Group on Hormonal Factors in Breast Cancer, 2012; Goswami et al., 2023). These variations are largely due to differences in study populations, study designs, and measurement methods, which contribute to significant between-study heterogeneity (NCBI Bookshelf, 2012).

While individual studies and conventional meta-analyses provide valuable insights, they often fail to adequately account for such heterogeneity, potentially resulting in overconfident estimates and misleading conclusions (IntHout, Ioannidis, & Borm, 2014). Although advanced methods like Knapp–Hartung adjusted random-effects meta-regression can address these issues by incorporating uncertainty in between-study variance, few studies have applied this approach to simultaneously evaluate multiple reproductive and familial covariates (Jackson, Law, & Rücker, 2017). Therefore, there is a notable gap in the literature for a methodologically rigorous analysis of existing evidence that can precisely assess the impact of key reproductive and familial factors on breast cancer risk while adequately accounting for between-study heterogeneity.

III. MATERIALS AND METHODS

3.1 Research Design

This study used a quantitative meta-regression approach to explore how certain reproductive and familial factors influence breast cancer risk. We specifically applied the Knapp–Hartung adjusted random-effects meta-regression, which allows us to combine findings from multiple studies while taking into account the differences between them—something that often occurs in breast cancer research due to variations in populations, study designs, and measurement methods.

By using this approach, we were able to examine several important factors at the same time, including menarche, menopause, ever breastfed and family history of breast cancer. The Knapp–Hartung adjustment helps make the results more trustworthy by producing conservative estimates and confidence intervals that account for the uncertainty in differences between studies.

This design makes it possible to draw stronger conclusions from existing studies and understand patterns that individual studies alone might not reveal. It is a practical and rigorous way to investigate how these key factors affect breast cancer risk across different populations.

3.2 Research Type

This study is a secondary research study that relies on the systematic analysis of data already published. It uses meta-regression as the main analytical method, which allows for the combination of results from multiple independent studies to identify patterns and associations between reproductive and familial factors and breast cancer risk.

Specifically, the study applies a Knapp–Hartung adjusted random-effects meta-regression, which is a rigorous statistical technique that accounts for variability between studies (heterogeneity) and produces more reliable and conservative estimates. By focusing on existing data this research allows for a broad evidence-based understanding of how factors such as menarche, menopause, ever breastfed and family history of breast cancer influence breast cancer risk.

3.3 Research Duration

The research was conducted over a period of 24 years, from 2000 to 2024.

3.4 Population of Study

The population for this study includes women from previously published epidemiological studies that examined the links between reproductive and familial factors and breast cancer risk. In particular, the analysis focused on studies that reported information on key factors such as menarche, menopause, ever breastfed and family history of breast cancer.

These studies included women from a variety of countries, age groups, and ethnic backgrounds, providing a broad and diverse perspective on breast cancer risk factors worldwide. Only studies with clearly defined populations and adequate sample sizes for calculating effect estimates and standard errors were included. Overall, data from 60 independent studies were analyzed, covering a wide range of participants to produce reliable results.

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3.5 Inclusion criteria

i. studies published between 2000 and 2024.
ii. Studies that provided data on at least one of the key variables of interest.
iii. Studies that reported quantitative effect measures such as odds ratios (ORs).
iv. Studies published in English.

3.6 Exclusion criteria

i. Studies that did not report effect estimates or lacked sufficient information to calculate standard errors.
ii. Studies reporting duplicate.
iii. Studies with poorly defined participant characteristics that could not be reliably compared across studies.
iv. Non-English publications.
v. Observational studies, including cohort and case-control designs that examined the association between reproductive or familial factors and breast cancer risk

3.7 Statistical Analysis

The data from the 60 selected studies were analyzed using a Knapp–Hartung adjusted random-effects meta-regression. This method was chosen because it allows us to combine results from multiple studies while properly accounting for differences between them, which are common in breast cancer research. The Knapp–Hartung adjustment makes the results more reliable by producing conservative confidence intervals and p-values that reflect the uncertainty in estimating variability between studies. The analysis focused on the effects of four key factors on breast cancer risk menarche, menopause, ever breastfed and family history of breast cancer. To measure variability between studies, we used between-study variance (τ^2) and the I^2 statistic, which show how much of the differences in effect sizes are due to real heterogeneity rather than chance.

Analyses were performed using R software and STATA with the metafor package for meta-analysis and meta-regression. Effect estimates and their standard errors from individual studies were used as inputs for the model. Statistical significance was set at $p < 0.05$, and results were reported with adjusted confidence intervals to ensure a conservative and trustworthy interpretation of the findings.

3.8 Knapp-Hartung Variance Estimator

The Knapp–Hartung adjusted random-effects meta-regression is an advanced method that accounts for between-study heterogeneity and provides more reliable confidence intervals and p-values than standard random-effects models (Knapp & Hartung, 2003; IntHout, Ioannidis, & Borm, 2014).

To account for between-study variance, the Knapp-Hartung variance estimator modifies the standard errors of the computed coefficients in meta-regression. When there is significant heterogeneity or a small number of studies, this technique yields a more reliable estimate of the variance. To estimate the between-study variance (τ^2), methods like Restricted Maximum Likelihood (REML) or Dersimonian-Laird Method is used and this estimate is used to adjust the weights in the meta-regression model.

3.8.1 Knapp-Hartung Variance Estimate for Coefficient

Let $\widehat{\beta_k}$ be the regression coefficient then the Knapp-Hartung variance estimator $\widehat{V_{KH}}(\widehat{\beta_k})$ is computed as:

$$\widehat{V_{KH}}(\widehat{\beta_k}) = \widehat{V_{FE}}(\widehat{\beta_k}) \text{ x } \left[1 + \frac{1}{n}\left(\frac{\sum_{i=1}^{n} w_i}{\sum_{i=1}^{n} w_i^2} - \frac{1}{n}\right)\right] \quad \ldots \quad (3.1)$$

Where:

$\widehat{V_{FE}}(\widehat{\beta_k})$ = Fixed-effects variance estimator for $\widehat{\beta_k}$.

w_i = weights for each study.

n = the number of studies.

3.8.2 Knapp-Hartung Adjustment for Confidence Interval (CI):

The confidence interval for the coefficient $\widehat{\beta_k}$ can be adjusted using Knapp-Hartung variance estimate:

$$CI_{KH}(\widehat{\beta_k}) = \widehat{\beta_k} \pm z_{\alpha/2}\sqrt{\widehat{V_{KH}}(\widehat{\beta_k})} \quad \ldots \quad (3.2)$$

Where:

$z_{\alpha/2}$ = Critical value from the standard normal distribution for the confidence level (1.96 or 95% CI).

3.8.3 Knapp-Hartung t-Test Statistic

The t-test statistic using the Knapp-Hartung variance estimator is:

$$t_{KH} = \frac{\widehat{\beta_k}}{\sqrt{\widehat{V_{KH}}(\widehat{\beta_k})}} \quad \ldots \quad (3.3)$$

Where:

$\widehat{\beta_k}$ = The estimated regression coefficient.

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$\sqrt{\widehat{V_{KH}}(\widehat{\beta_k})}$ = The standard error from Knapp-Hartung variance.

3.8.4 Random-effects meta-regression

According to Berkey et al.(1995) random-effects meta-regression model may be defined as:

$\widehat{\phi_i} = x_i\beta + u_i + \varepsilon_i \ \ldots$ (3.4)

Where:

ϕ_i = Estimated effect sizes.

x_i = n x (p + 1) matrix of the predictors.

β = (p + 1) x 1 vector of coefficients.

$u_i \sim N(0, \tau^2)$.

$\varepsilon_i \sim N(0, \widehat{\sigma_i^2})$.

Random-effects meta-regression first estimate the between-study variance, τ^2 and the regression coefficients are then estimated via weighted least squares.

$\widehat{\beta^*} = (X'W^*X)^{-1} X'W^*\hat{\phi} \ \ldots$ (3.5)

Where:

$W^* = diag(w_1^*, w_2^*, \ldots, w_k^*)$ and $w_i^* = (1/\sigma_i^2 + \widehat{\tau^2})$.

Or equivalently

$Effect\ size_i = \beta_0 + \beta_1 Covariate_{i1} + \beta_2 Covariate_{i2} + \ldots + \beta_p Covariate_{ip} + u_i + \varepsilon_i$

Where;

$Effect\ size_i$ = The effect size for study i.

β_0 = The intercept of the meta-regression model.

$\beta_1, \beta_2, \ldots, \beta_p$ = Are the regression coefficients for the predictor variables ($Covariate_{i1}, Covariate_{i2}, \ldots, Covariate_{ip}$).

u_i = The random effect specific to study i, which accounts for the between-study variability in the effect size.

ε_i = The residual error for study i, assumed to be normally distributed with zero mean and variance σ^2.

3.8.5 The Variance Components

The total variance of the effect size is decomposed into two in random-effects model.

i. Between-study variance (τ^2), which is the variability in the true effect sizes across studies.
ii. Within-study variance (σ^2), which is the variability within each study.

The variance of the effect size for study i is given as:

$\text{Var}(\phi_i) = \sigma^2 + \tau^2 \ \ldots$ (3.6)

The weighted regression is estimated from the random-effects meta-regression model since the model accounts for both within-study and between-study variances.

3.8.6 The Vector of Estimated Coefficients

In random-effects meta-regression, the vector of estimated regression coefficients is:

$$\widehat{\beta^*} = \begin{bmatrix} \hat{\beta}_0 \\ \hat{\beta}_1 \\ \hat{\beta}_2 \\ \vdots \\ \widehat{\beta_p} \end{bmatrix}$$

Where:

$\widehat{\beta_0}$ = Estimated intercept.

$\widehat{\beta_1}, \widehat{\beta_2}, \ldots, \widehat{\beta_p}$ = Estimated coefficients for the covariates variables.

The weight for each study in random-effects meta-regression is computed as:

$w_i = \frac{1}{\sigma^2 + \tau^2} \ \ldots$ (3.7)

Where:

σ^2 = The within-study variance.

τ^2 = The between- study variance.

Both the σ^2 and τ^2 need to be estimated either from Restricted Maximum Likelihood (REML), Dersimonian-Laird Method, Method of Moment or Empirical Bayes Methods.

IV. DATA ANALYSIS AND RESULTS

Table 4.1 showing results for Knapp-Hartung Adjusted Random-Effects Meta-Regression.

Knapp–Hartung Adjusted Random-Effects Meta-Regression Results

	Estimate	Std. Error	t value	df	P(>|t|)
Age at Menarche	0.1116	0.0586	1.90	56	0.063
Ever Breastfed	-0.4135	0.1106	-3.74	56	0.001
Age at Menopause	0.1082	0.0464	2.33	56	0.024
Family History	0.2435	0.0958	2.54	56	0.015

The Knapp–Hartung adjusted random-effects meta-regression revealed that ever breastfed was significantly associated with a lower outcome (β = -0.414, p = 0.001), suggesting that individuals who had ever breastfed tended to have a reduced risk of developing breast cancer compared to those who had not. Menopause (β = 0.108, p = 0.024) and family history (β = 0.244, p = 0.015) were significantly positively associated with the outcome, indicating that later menopause and having a family history were linked to increased risk of breast cancer. Menarche showed a positive but non-significant association (β = 0.112, p = 0.063), suggesting a possible trend toward higher risk with later menarche.

4.1 Discussion

The Knapp–Hartung adjusted random-effects meta-regression demonstrated that ever breastfed was significantly associated with a lower outcome (β = -0.414, p = 0.001), indicating a protective effect that may be mediated by hormonal or physiological mechanisms. However, menopause (β = 0.108, p = 0.024) and a positive family history (β = 0.244, p = 0.015) were significantly associated with higher outcomes, underscoring the influence of prolonged hormonal exposure and genetic predisposition in elevating the risk of breast cancer. Menarche showed a positive but non-significant association (β = 0.112, p = 0.063), suggesting a potential trend toward increased risk with later menarche that warrants further study.

5.1 Summary

Our analysis demonstrated that ever breastfed was significantly associated with a lower risk, suggesting a protective effect that may be caused by hormonal and physiological changes associated with lactation. However, women who experienced menopause and those with a family history of breast cancer were found to have higher risk, highlighting the influence of prolonged hormonal exposure and genetic predisposition on susceptibility. Menarche showed a positive but non-significant trend toward increased risk, indicating that its impact may be modest or variable. Taken together, these findings underscore the importance of both reproductive history and familial factors in shaping breast cancer risk, with ever breastfed providing a potential protective benefit, while menopause and genetic predisposition appear to contribute to increased vulnerability.

5.2 Conclusion

The results of this Knapp–Hartung adjusted random-effects meta-regression indicate that ever breastfed is significantly associated with a lower risk, suggesting a protective effect that may be caused by hormonal and physiological changes. However, menopause and a positive family history of breast cancer were significantly associated with higher risk, highlighting the influence of prolonged hormonal exposure and genetic predisposition on susceptibility. Menarche showed a positive but non-significant trend toward increased risk, suggesting that its role may be less pronounced or variable across populations and warrants further investigation. Overall, these findings indicates the importance of considering both reproductive history and familial factors when evaluating risk, and they provide further evidence for the potential benefits of breastfeeding as a modifiable protective factor.

5.3 Recommendation

Based on these findings, public health initiatives should continue to promote and support breastfeeding as a protective factor against risk, while healthcare providers should incorporate reproductive history including menarche, menopause and family history of breast cancer into individual risk assessments to identify those at higher risk of developing breast cancer and further research is warranted to clarify the role of age at menarche.

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