Herpes Zoster Vaccination and Risk of Braest Cancer in Women Undergoing Mammographic Screening: A TriNetX Real-World Analysis

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Background

Herpes Zoster vaccination is routinely recommended for adults aged ≥50 years to prevent shingles and its complications. To date, no evidence exists that herpes zoster vaccination reduces breast cancer (BC) risk. Observed associations between vaccinations and lower cancer incidence in some real-world studies may reflect differences in healthcare behavior, immune status, or unmeasured confounding rather than a true protective effect. We investigated whether vaccination with Shingrix®, a recombinant, adjuvanted herpes zoster vaccine, might influence the risk of subsequent BC diagnosis in women undergoing routine mammographic screening.

Methods

We performed a retrospective real-world study using the TriNetX Global Collaborative Network. We included women aged ≥50 years undergoing mammographic screening. The initial cohorts included 5,696 vaccinated women and 1,116,138 unvaccinated women. The vaccinated cohort comprised women who received Shingrix® after screening, while the unvaccinated cohort included women who underwent screening but were never vaccinated against herpes zoster. Patients with a prior diagnosis of BC before the observation period were excluded. Propensity score matching (PSM) was performed based on age, race, ethnicity, Charlson Comorbidity Index, BMI, smoking, alcohol-related disorders, genetic susceptibility to malignancy, and systemic corticosteroid use, resulting in 5,680 women per group (Figure 1.). Additionally, multivariable Cox proportional hazards models were applied, adjusting for age, genetic susceptibility, and alcohol-related disorders, with a separate analysis restricting the unvaccinated group to academic medical centers. The observation period extended to 20 years in the TriNetX network. The outcome was the incidence of BC, analyzed as time-to-event from the index date of vaccination or screening

Results

After matching, 5,680 vaccinated women were compared to an equal number of unvaccinated women. The cumulative incidence of BC was significantly lower among vaccinated patients, with 6.4% developing BC compared to 10.7% in the unvaccinated group (risk difference −4.2%, 95% CI −5.2% to −3.2%; p<0.001). Cox regression in the unmatched cohorts confirmed this association, yielding a hazard ratio of 0.617 (95% CI, 0.557–0.684; p<0.0001) when comparing vaccinated patients to the overall unvaccinated group. When restricting the analysis to unvaccinated women treated at academic centers, the association appeared even stronger, with a hazard ratio of 0.447 (95% CI, 0.404–0.496; p<0.0001). However, the absolute differences in incidence rates remained modest.

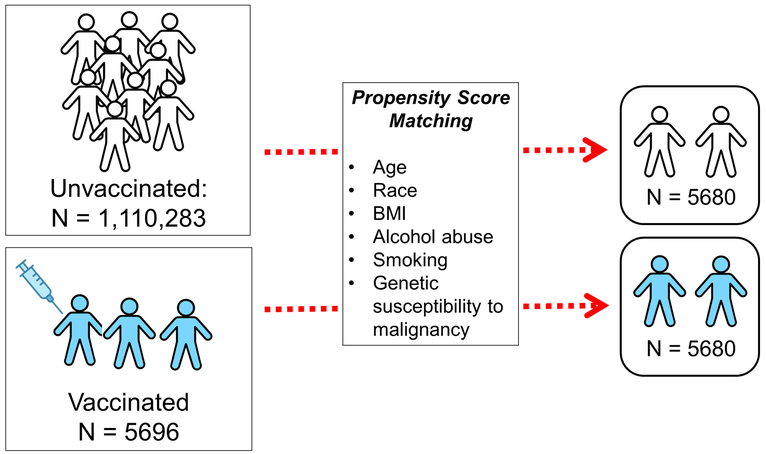
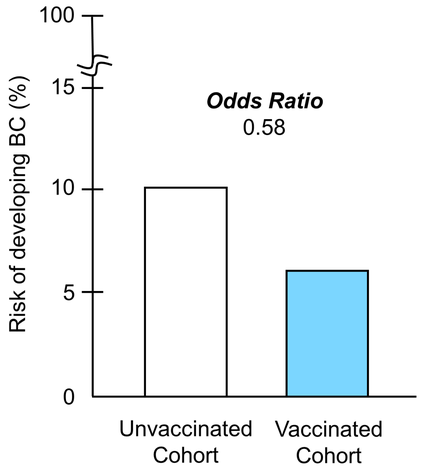


Figure 1. Study Design



Conclusions

In this large real-world analysis, vaccination with Shingrix® was associated with a significantly reduced risk of BC diagnosis among women undergoing mammographic screening. However, the observed 40–45% risk reduction is difficult to explain biologically and may result from healthy user bias, residual confounding related to factors such as family history or hormonal therapy use, or surveillance bias leading to earlier detection in vaccinated women. These findings should be interpreted as hypothesis-generating and require confirmation in prospective studies.

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