

PRESENTED AT:

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Disclosure Information

Relationships with Companies

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Other Relationships: Research to Practice, Clinical Care Options, Physician's Education Resource

Uncompensated Relationships: Epic Sciences, Merck, Pfizer, Daiichi Sankyo

Presented at ASCO 2020

Comprehensive breast cancer (BC) risk assessment for *CHEK2* carriers incorporating a polygenic risk score (PRS) and the Tyrer-Cuzick (TC) model

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Germline Pathogenic Variants (PV) in *CHEK2* are Common and Lead to a Moderately Increased Risk for Female Breast Cancer

- Lifetime breast cancer risk estimates range from 23% to 48%
- Close to 1% of individuals tested with a hereditary cancer panel carry a *CHEK2* PV, 65% of which are 1100del, a European founder PV
- Consistent with the >20% estimated lifetime breast cancer risk, current NCCN guidelines for management of *CHEK2* PV carriers include consideration of annual breast MRI screening beginning at age 40

Breast Cancer Risks for *CHEK2* Carriers are Modified by Other Factors

- Previous studies have shown that breast cancer risk in women with PV in hereditary breast cancer risk genes, including *CHEK2*, is modified by:
 - Family history
 - Clinical factors related to lifetime estrogen exposure
 - Multiple low penetrance breast cancer risk variants (SNPs), which we have integrated into an 86-SNP Polygenic Risk Score (PRS)

Goal: Development of a comprehensive risk prediction model for women with *CHEK2* PV to more precisely estimate risk incorporating the 86-SNP PRS and the Tyrer-Cuzick model.

Specific Aims

- Expand the Tyrer-Cuzick model (v7) to incorporate *CHEK2* risks
- Incorporate PRS into the *CHEK2*/Tyrer-Cuzick model
- Evaluate risk stratification in *CHEK2 PV* carriers who were not included in risk model development

Methods: *CHEK2* + Tyrer-Cuzick Model Development

Study population: 355,429 women of European ancestry referred for hereditary cancer testing

Exclusions

- Homozygous/compound het
- DCIS, LCIS, or hyperplasia without subsequent BC diagnosis

	<i>CHEK2</i> PV Carriers*	Non-Carriers
Total Patients	4,286	351,143
Age Range	18-83	18-84
Median Age	46	47
Diagnosed with BC	1,583 (37%)	83,257 (24%)
≥ 1 FDR with BC	1,856 (43%)	123,915 (35%)

**CHEK2* variants I157T and S428 are not considered PV in this analysis

Methods: *CHEK2* + Tyrer-Cuzick Model Development

Considerations for combining *CHEK2* with Tyrer-Cuzick:

CHEK2 Risk

- Is 1100delC equivalent to other PVs?
- Is *CHEK2* risk age dependent?

Confounding:

- Are Tyrer-Cuzick factors correlated with *CHEK2* status? (e.g., BC family history)



Important to prevent double counting of risk

Interaction:

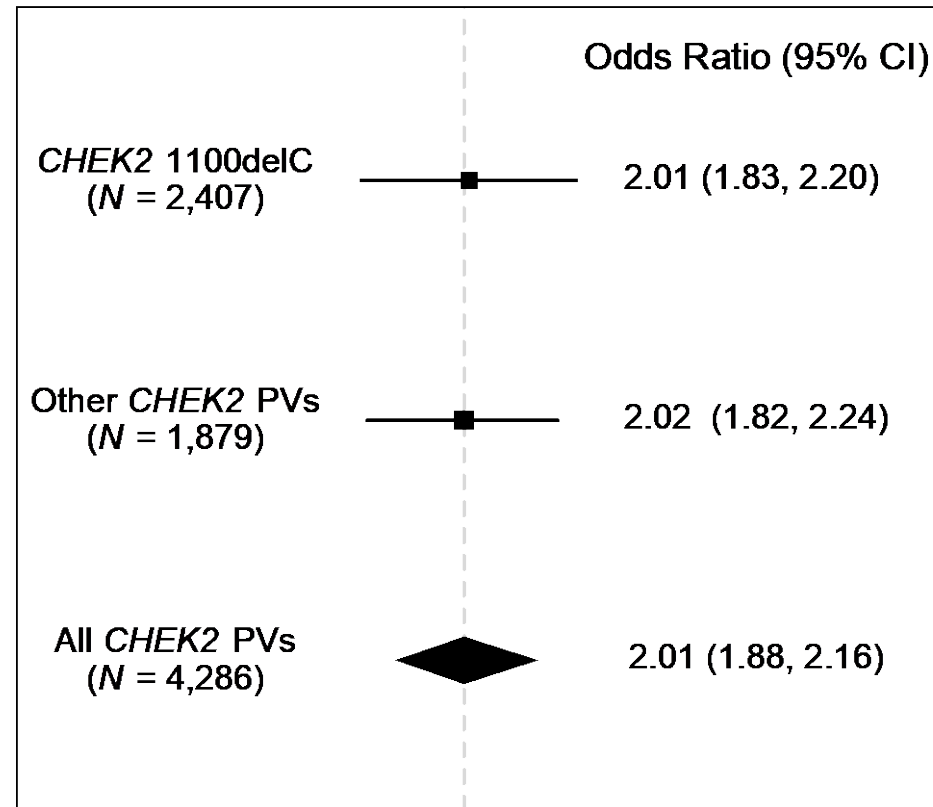
- Do factors in Tyrer-Cuzick confer the same risk to *CHEK2* carriers as non-carriers?



*Validity of Tyrer-Cuzick for *CHEK2* carriers*

Methods: *CHEK2* + Tyrer-Cuzick Model Development

1100delC was equivalent to other *CHEK2* PVs in terms of breast cancer risk

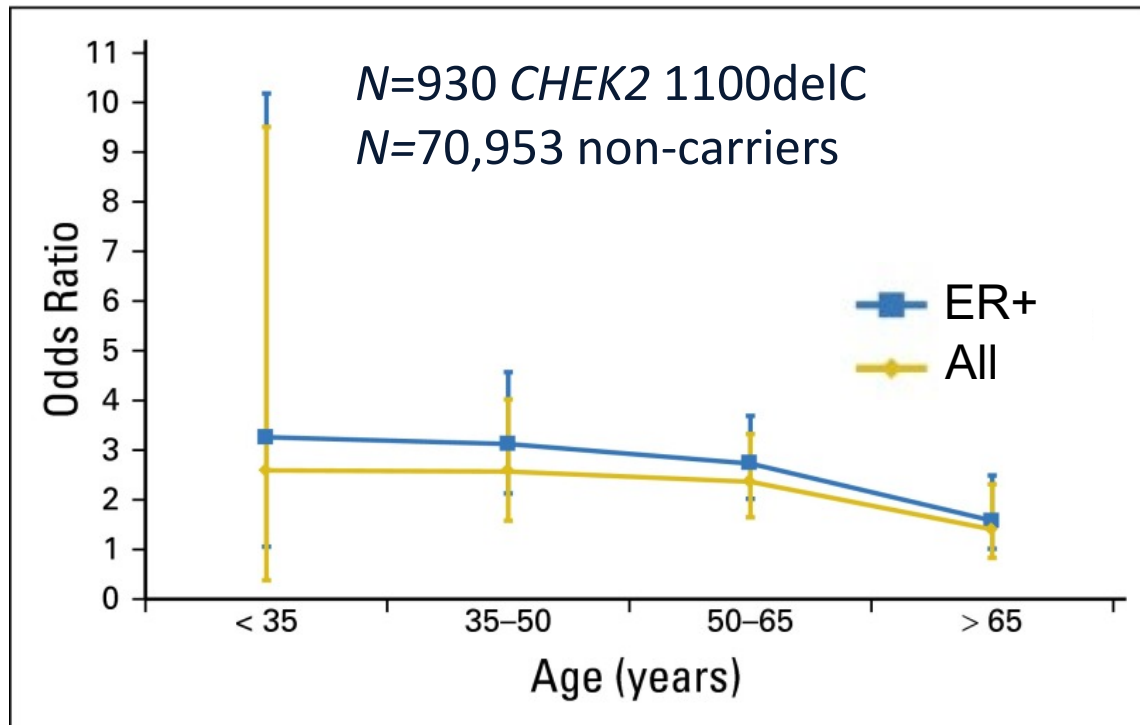


Odds ratios derived from multivariable logistic regression models predicting breast cancer based on *CHEK2* PV status and adjusted for age, Ashkenazi ancestry, personal and familial cancer history

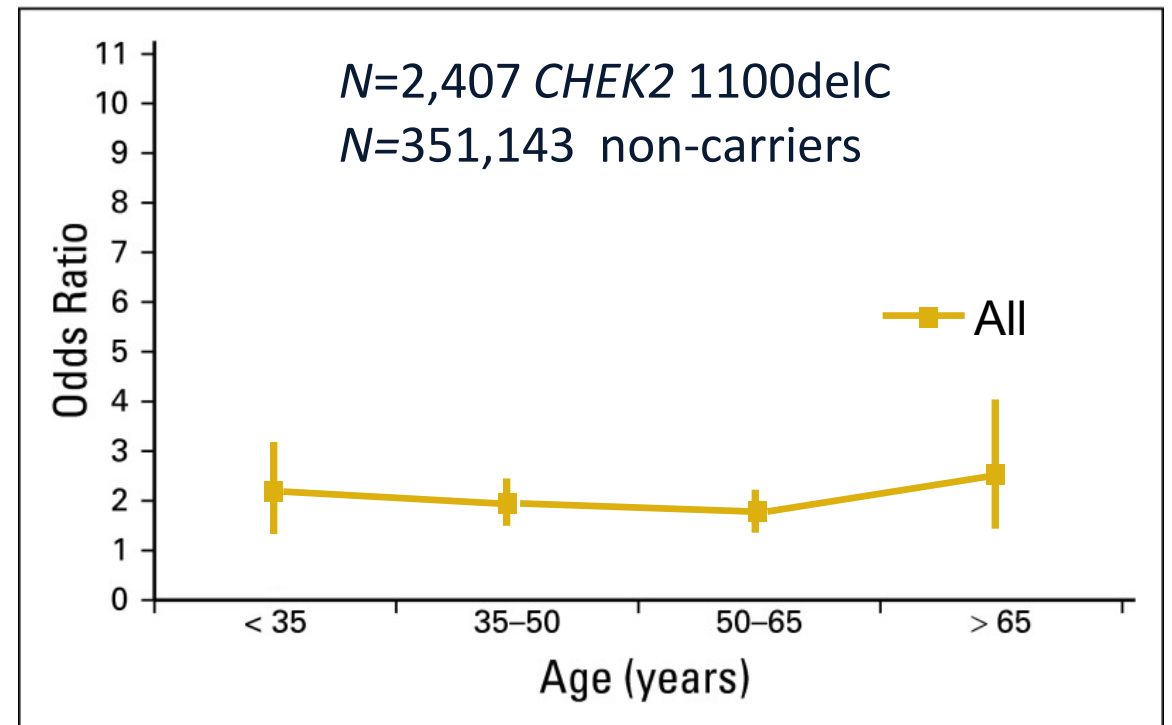
Methods: *CHEK2* + Tyrer-Cuzick Model Development

- *CHEK2* risks were consistent with prior literature
- Modest age dependence reported in prior literature for 1100delC was not reproduced

Schmidt et al., 2016



This study



Methods: *CHEK2* + Tyrer-Cuzick Model Development

CHEK2 was combined with the Tyrer-Cuzick model according to a Fixed-Stratified (FS) method¹ that prevents double-counting of information from correlated risk factors in a manner equivalent to full multivariable co-estimation. Briefly,

- Any risk factor showing correlation with *CHEK2* status, e.g., family history (FH), was modelled as a predictor of breast cancer (BC) in logistic regression

$$\text{Model 1: BC} \sim \beta_1 \times \text{FH}$$

- The association of *CHEK2* with BC was estimated from a model with the effect of FH fixed

$$\text{Model 2: BC} \sim \text{offset}(\beta_1 \times \text{FH}) + \beta_2 \times \text{CHEK2}$$

- Unaffected women (carriers and non-carriers) were stratified according to FH severity
- Absolute remaining lifetime risk for a woman in FH strata k at t years of age is

$$1 - [1 - \text{Tyrer-Cuzick}(t)]^{\exp\{\beta_2 \times \text{CHEK2} + C_k\}}$$

where C_k was calculated to preserve the average Tyrer-Cuzick risk within strata k after incorporating *CHEK2*

$$C_k = -\ln(E[\exp\{\beta_2 \times \text{CHEK2}\}]), \text{ with expected value taken across strata } k$$

Methods: *CHEK2* + Tyrer-Cuzick Model Development

- *CHEK2* status was strongly associated with family history of BC (p-value $<10^{-14}$).



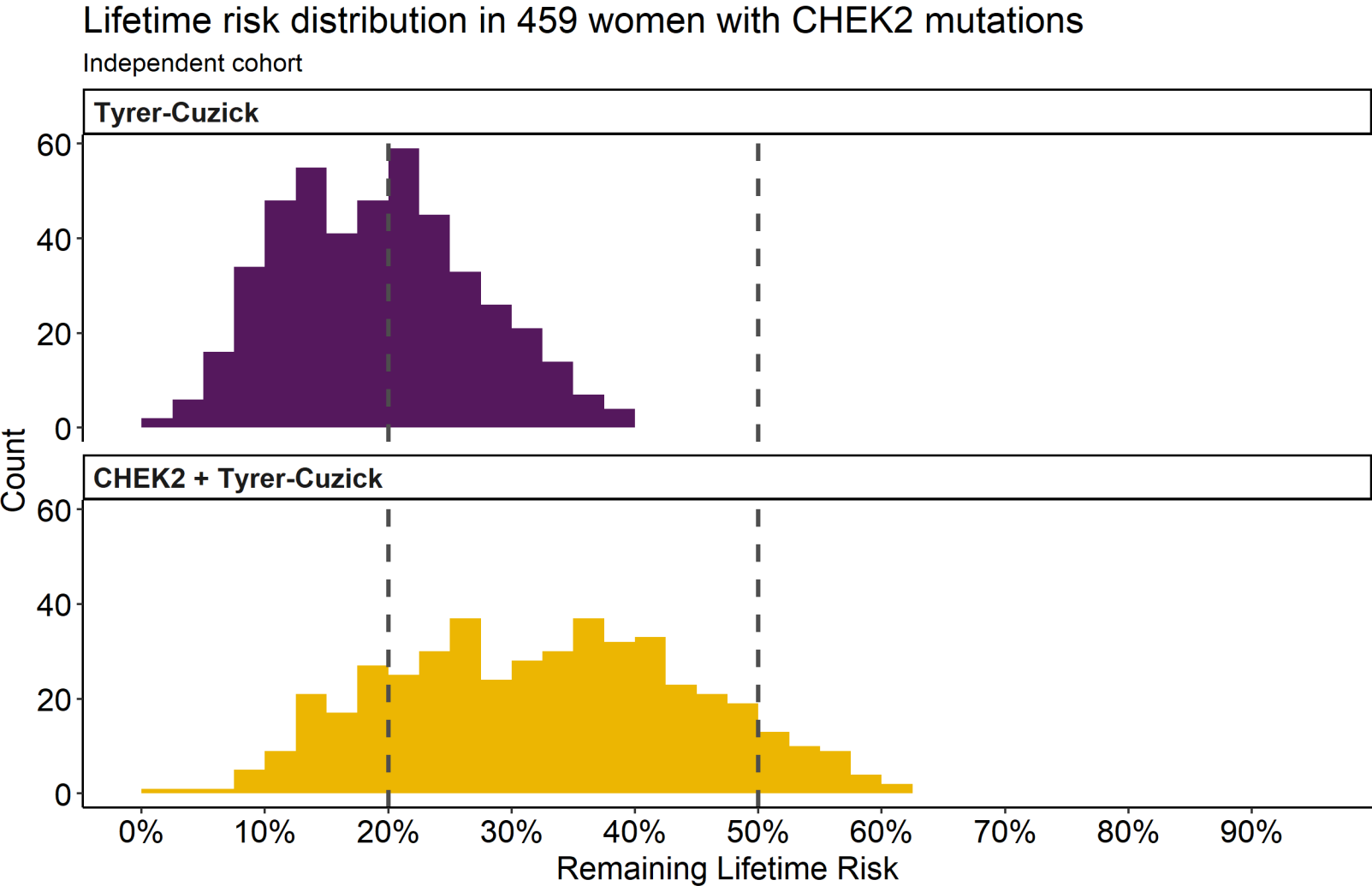
Combined according to the Fixed-Stratified method to avoid double counting

- No other Tyrer-Cuzick risk factors showed evidence of association.
- No Tyrer-Cuzick risk factors showed evidence of interaction with *CHEK2* status



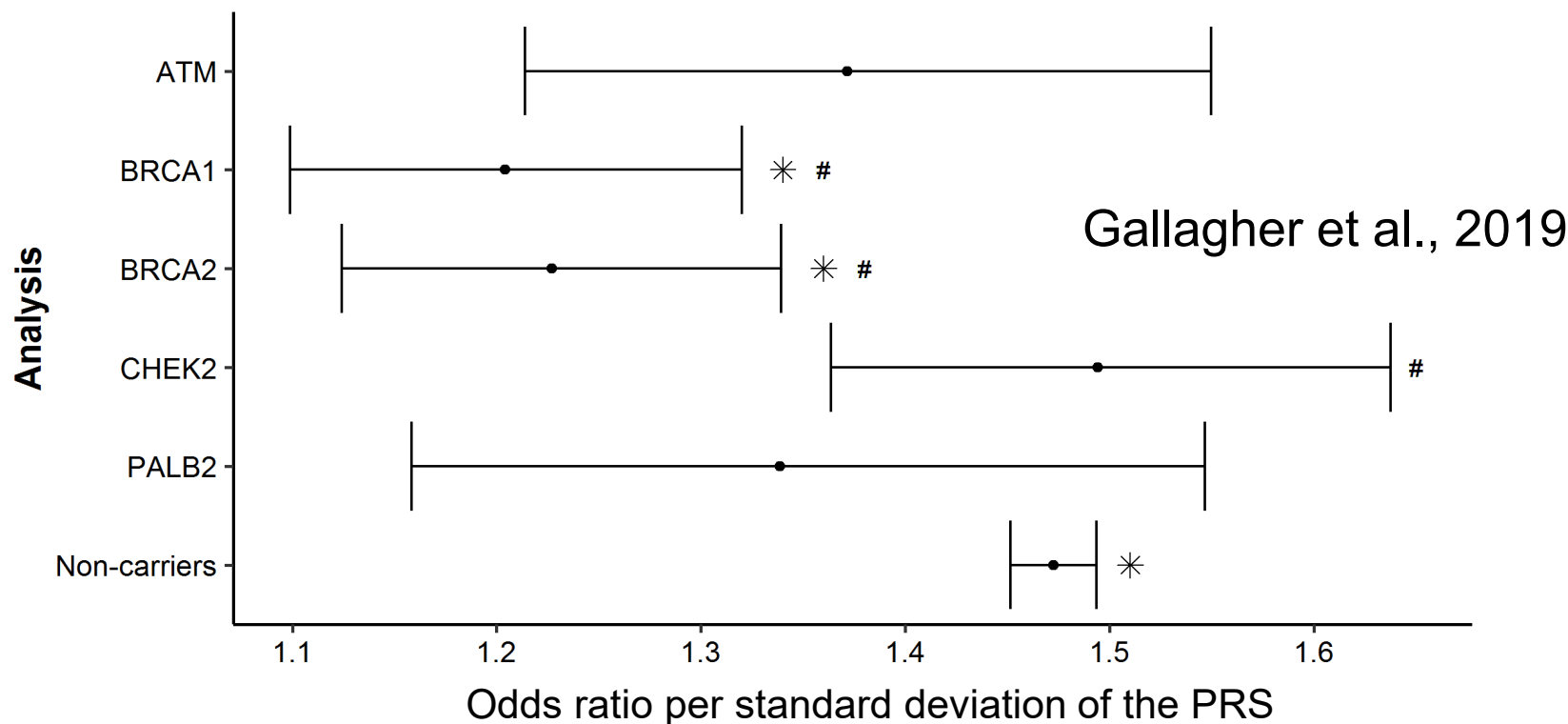
Factors confer the same risk to *CHEK2* carriers as non-carriers

Results: Risk Stratification



Methods: Incorporate PRS

PRS stratification for *CHEK2* carriers is comparable to non-carriers



This forest plot displays the standardized OR for the association between PRS and personal BC history along with 95% CI for carriers of each gene and non-carriers.
* denotes a significant difference ($p < 1 \times 10^{-4}$) between non-carriers and individuals with a PV in *BRCA1/BRCA2*.
denotes a significant difference ($p < .01$) between individuals with *CHEK2* mutations and those with a PV in *BRCA1/2*.

Methods: Incorporate PRS

- PRS is associated with family history of breast cancer, but not with any other Tyrer-Cuzick risk factors.



Combined with multivariable adjustment to avoid double counting of risk information

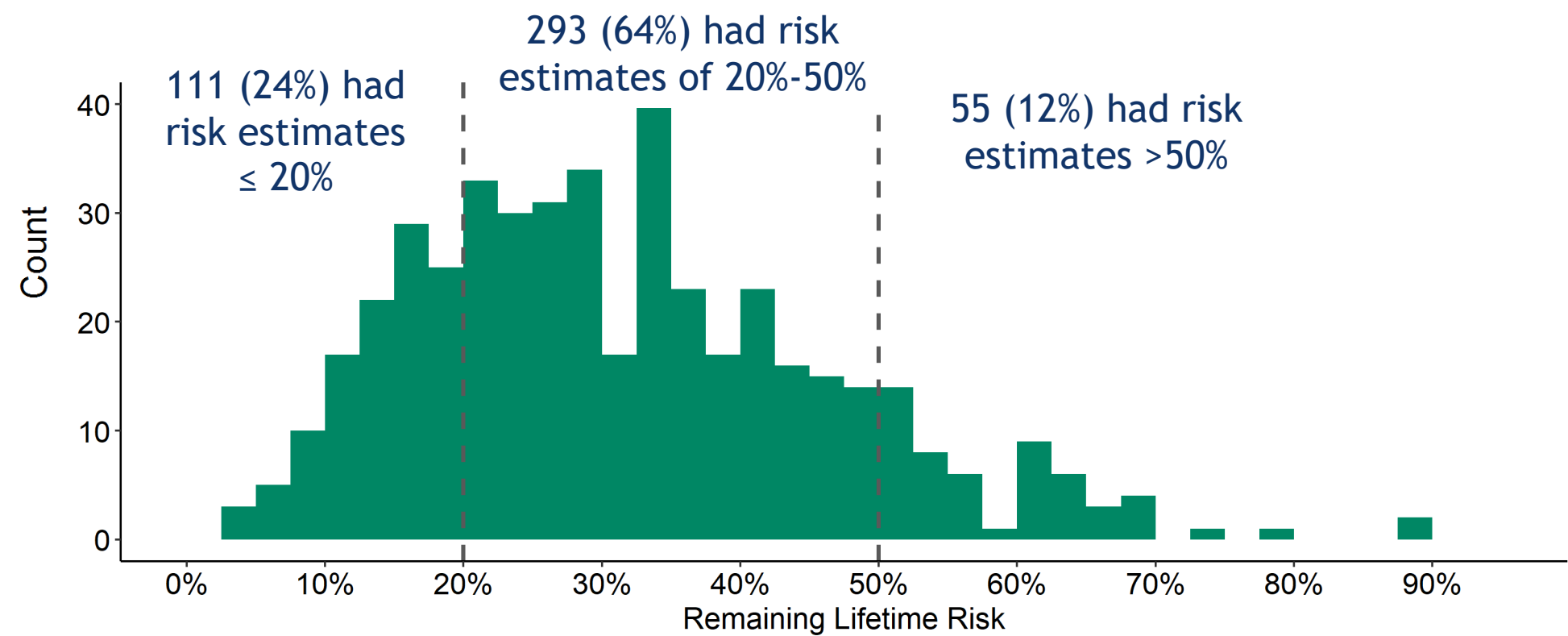
- No Tyrer-Cuzick risk factors showed evidence of interaction with PRS after multiple testing correction (marginal interaction with family history).



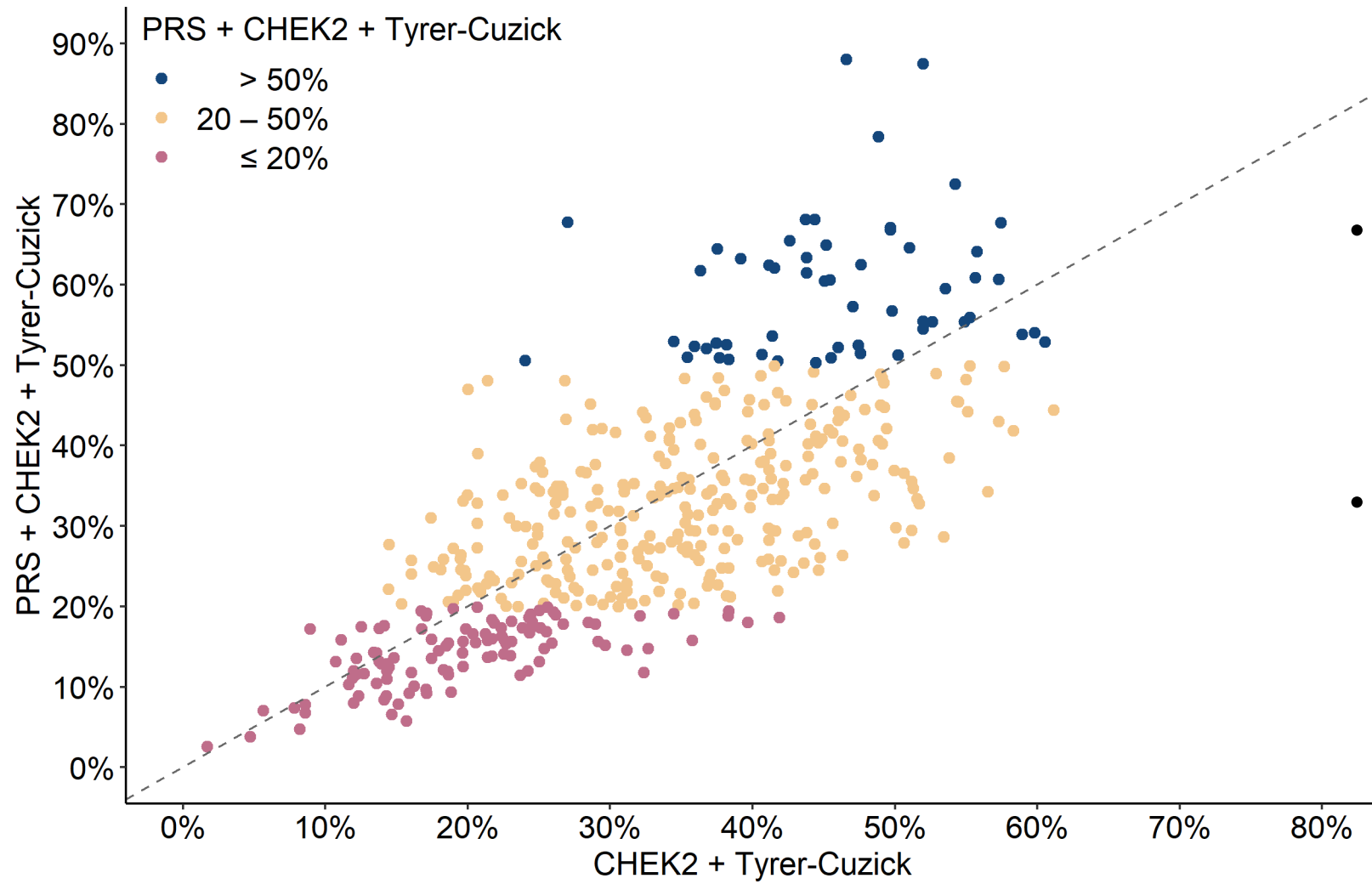
Factors confer essentially the same risk to women with high PRS as low PRS

Results: Risk Stratification

Risk Based on PRS + *CHEK2* + Tyrer-Cuzick



Results: Risk Stratification



- Risk stratification was increased by incorporating PRS into the model based on *CHEK2* + Tyrer-Cuzick
- Risk estimates can increase or decrease significantly due to PRS

Limitations

- Analyses were based on data from women referred for hereditary cancer testing; clinical information from test request forms may have been incomplete or inaccurate.
- Further studies are necessary to characterize polygenic breast cancer risk for women of non-European ancestry.
- Additional work is needed to incorporate other important risk factors such as breast density.

Conclusions

- Personalized risk prediction is important for *CHEK2* PV carriers because these patients have a wide spectrum of risk that is influenced by many factors.
- Comprehensive risk assessment could improve stratification and inform individualized decision-making for screening and prevention strategies.