

Supplemental Online Content

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This supplemental material has been provided by the authors to give readers additional information about their work.

eTable1: Comparison of *CHEK2* p.I157T to WT and *CHEK2* monoallelic pathogenic variants

| Characteristic | WT | | <i>CHEK2</i> monoallelic PV* | | p.I157T | | p.I157T vs. WT | | p.I157T vs. <i>CHEK2</i> PV* | |
|----------------------------------|------------|-------|------------------------------|-------|------------|-------|------------------|-----------------|------------------------------|-----------------|
| | No. | % | No. | % | No. | % | OR (95% CI) | P value | OR (95% CI) | P value |
| Age at first breast cancer (IQR) | 50 (43-59) | | 47 (41-56) | | 49 (42-57) | | | 0.06 | | 0.02 |
| Age at first cancer (IQR) | 49 (42-58) | | 47 (40-56) | | 48 (41-58) | | | 0.13 | | 0.03*** |
| Race, ethnicity and ancestry | | | | | | | | | | |
| African American/Black | 1815 | 5.5% | 37 | 1.7% | 3 | 0.3% | 0.04 (0.01-0.12) | <.001 | 0.16 (0.03-0.51) | <.001 |
| Ashkenazi Jewish | 2247 | 6.8% | 92 | 4.2% | 34 | 3.4% | 0.38 (0.26-0.54) | <.001 | 0.73 (0.47-1.11) | 0.15 |
| Asian | 1071 | 3.2% | 20 | 0.9% | 0 | 0.0% | 0 (0-0.09) | <.001 | 0 (0-0.4) | <.001 |
| White | 21907 | 66.3% | 1707 | 78.7% | 862 | 86.9% | | | | |
| Hispanic | 1582 | 4.8% | 66 | 3.0% | 6 | 0.6% | 0.1 (0.04-0.21) | <.001 | 0.18 (0.06-0.42) | <.001 |
| Other | 4409 | 13.4% | 246 | 11.4% | 87 | 8.8% | 0.5 (0.4-0.63) | <.001 | 0.7 (0.53-0.91) | 0.006 |
| Any Cancer | | | | | | | 1.19 (1.03-1.38) | 0.015 | 0.84 (0.7-1) | 0.04*** |
| Yes | 23065 | 69.8% | 1664 | 76.8% | 728 | 73.4% | | | | |
| No | 9969 | 30.2% | 504 | 23.3% | 264 | 26.6% | | | | |
| No. of primary cancer | | | | | | | | | | |
| 0 | 9969 | 30.2% | 504 | 23.3% | 264 | 26.6% | | | | |
| 1 | 18498 | 56.0% | 1348 | 62.2% | 591 | 59.6% | | | | |
| >1 | 4567 | 13.8% | 316 | 14.6% | 137 | 13.8% | | 0.046 | | 0.12 |
| Breast cancer** | | | | | | | 1.21 (1.06-1.39) | 0.005*** | 0.66 (0.56-0.78) | <.001 |
| Yes | 16029 | 52.7% | 1339 | 67.1% | 524 | 57.7% | | | | |
| No | 13584 | 44.6% | 620 | 31.1% | 366 | 40.3% | | | | |
| Bilateral breast cancer** | | | | | | | 1.52 (1.23-1.89) | <.001 | 0.77 (0.60-0.98) | 0.03*** |
| Yes | 2228 | 7.3% | 273 | 13.7% | 98 | 10.8% | | | | |
| No | 27345 | 89.9% | 1683 | 84.4% | 789 | 86.9% | | | | |
| Colorectal cancer | | | | | | | 0.8 (0.61-1.04) | 0.09 | 1.29 (0.92-1.79) | 0.13 |
| Yes | 2575 | 7.8% | 109 | 5.0% | 63 | 6.4% | | | | |
| No | 29550 | 89.5% | 2015 | 92.9% | 904 | 91.1% | | | | |
| Kidney cancer | | | | | | | 1.71 (0.84-3.15) | 0.11 | 0.67 (0.31-1.35) | 0.27 |
| Yes | 214 | 0.7% | 36 | 1.7% | 11 | 1.1% | | | | |

| | | | | | | | | | | |
|-------------------|-------|-------|------|-------|-----|-------|------------------|------|------------------|------|
| No | 31896 | 96.6% | 2088 | 96.3% | 956 | 96.4% | | | | |
| Melanoma | | | | | | | 0.68 (0.44-1) | 0.05 | 0.95 (0.57-1.54) | 0.91 |
| Yes | 1259 | 3.8% | 60 | 2.8% | 26 | 2.6% | | | | |
| No | 30854 | 93.4% | 2064 | 95.2% | 941 | 94.9% | | | | |
| Pancreatic cancer | | | | | | | 0.72 (0.38-1.25) | 0.28 | 1.43 (0.65-3.04) | 0.35 |
| Yes | 597 | 1.8% | 20 | 0.9% | 13 | 1.3% | | | | |
| No | 31517 | 95.4% | 2104 | 97.1% | 954 | 96.2% | | | | |
| Thyroid cancer | | | | | | | 1.4 (0.92-2.04) | 0.09 | 0.86 (0.53-1.34) | 0.52 |
| Yes | 696 | 2.1% | 74 | 3.4% | 29 | 2.9% | | | | |
| No | 31416 | 95.1% | 2050 | 94.6% | 938 | 94.6% | | | | |

**CHEK2* PV – pathogenic and likely pathogenic variants in *CHEK2* excluding the lower risk *CHEK2* variants: p.I157T, p.S428F and p.T476M

**Denominator for sex-specific cancers was total number of females with given variant for breast and bilateral breast cancer.

***After Bonferroni correction, this P value is not significant.

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio; PV, pathogenic or likely pathogenic variant; WT, wildtype

eTable2: Comparison of *CHEK2* p.S428F to WT and *CHEK2* monoallelic pathogenic variants

| Characteristic | WT | | <i>CHEK2</i> monoallelic PV* | | p.S428F | | p.S428F vs. WT | | p.S428F vs. <i>CHEK2</i> PV* | |
|----------------------------------|------------|-------|---------------------------------|-------|---------------|-------|--------------------|-------------|------------------------------|---------|
| | No. | % | No. | % | No. | % | OR (95% CI) | P value | OR (95% CI) | P value |
| Age at first breast cancer (IQR) | 50 (43-59) | | 47 (41-56) | | 52 (44-61) | | | 0.07 | | <.001 |
| Age at first cancer (IQR) | 49 (42-58) | | 47 (40-56) | | 50 (43-59.75) | | | 0.09 | | <.001 |
| Race, ethnicity and ancestry | | | | | | | | | | |
| African American/Black | 1815 | 5.5% | 37 | 1.7% | 0 | 0.0% | 0 (0-0.82) | 0.02 | 0 (0-3.3) | 0.63 |
| Ashkenazi Jewish | 2247 | 6.8% | 92 | 4.2% | 245 | 75.6% | 42.6 (31.66-58.23) | <.001 | 80.91 (55.95-118.43) | <.001 |
| Asian | 1071 | 3.2% | 20 | 0.9% | 0 | 0.0% | 0 (0-1.4) | 0.11 | 0 (0-6.37) | >.99 |
| White | 21907 | 66.3% | 1707 | 78.7% | 56 | 17.3% | | | | |
| Hispanic | 1582 | 4.8% | 66 | 3.0% | 1 | 0.3% | 0.25 (0.01-1.44) | 0.18 | 0.46 (0.01-2.77) | 0.72 |
| Other | 4409 | 13.4% | 246 | 11.4% | 22 | 6.8% | 1.95 (1.13-3.25) | 0.01 | 2.72 (1.55-4.63) | <.001 |
| Any Cancer | | | | | | | 0.72 (0.57-0.9) | 0.004*** | 0.5 (0.39-0.65) | <.001 |
| Yes | 23065 | 69.8% | 1664 | 76.8% | 202 | 62.4% | | | | |
| No | 9969 | 30.2% | 504 | 23.3% | 122 | 37.7% | | | | |
| No. of primary cancer | | | | | | | | | | |
| 0 | 9969 | 30.2% | 504 | 23.3% | 122 | 37.7% | | | | |
| 1 | 18498 | 56.0% | 1348 | 62.2% | 166 | 51.2% | | | | |
| >1 | 4567 | 13.8% | 316 | 14.6% | 36 | 11.1% | | 0.02 | | <.001 |
| Breast cancer** | | | | | | | 1.08 (0.86-1.37) | 0.51 | 0.59 (0.46-0.76) | <.001 |
| Yes | 16029 | 52.7% | 1339 | 67.1% | 161 | 54.8% | | | | |
| No | 13584 | 44.6% | 620 | 31.1% | 126 | 42.9% | | | | |
| Bilateral breast cancer** | | | | | | | 0.87 (0.55-1.39) | 0.56 | 0.44 (0.27-0.71) | <.001 |
| Yes | 2228 | 7.3% | 273 | 13.7% | 19 | 6.5% | | | | |
| No | 27345 | 89.9% | 1683 | 84.4% | 268 | 91.2% | | | | |
| Colorectal cancer | | | | | | | 0.26 (0.1-0.55) | <.001 | 0.42 (0.16-0.91) | 0.02*** |
| Yes | 2575 | 7.8% | 109 | 5.0% | 7 | 2.2% | | | | |
| No | 29550 | 89.5% | 2015 | 92.9% | 307 | 94.8% | | | | |
| Kidney cancer | | | | | | | 1.44 (0.29-4.3) | 0.47 | 0.56 (0.11-1.79) | 0.47 |
| Yes | 214 | 0.7% | 36 | 1.7% | 3 | 0.9% | | | | |

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|-------------------|-------|-------|------|-------|-----|-------|------------------|------|------------------|------|
| No | 31896 | 96.6% | 2088 | 96.3% | 311 | 96.0% | | | | |
| Melanoma | | | | | | | 0.97 (0.5-1.73) | >.99 | 1.37 (0.66-2.6) | 0.37 |
| Yes | 1259 | 3.8% | 60 | 2.8% | 12 | 3.7% | | | | |
| No | 30854 | 93.4% | 2064 | 95.2% | 302 | 93.2% | | | | |
| Pancreatic cancer | | | | | | | 0.34 (0.04-1.24) | 0.14 | 0.67 (0.08-2.8) | >.99 |
| Yes | 597 | 1.8% | 20 | 0.9% | 2 | 0.6% | | | | |
| No | 31517 | 95.4% | 2104 | 97.1% | 312 | 96.3% | | | | |
| Thyroid cancer | | | | | | | 1.03 (0.41-2.16) | 0.85 | 0.63 (0.24-1.39) | 0.31 |
| Yes | 696 | 2.1% | 74 | 3.4% | 7 | 2.2% | | | | |
| No | 31416 | 95.1% | 2050 | 94.6% | 307 | 94.8% | | | | |

**CHEK2* PV – pathogenic and likely pathogenic variants in *CHEK2* excluding the lower risk *CHEK2* variants: p.I157T, p.S428F and p.T476M.

**Denominator for sex-specific cancers was total number of females with given variant for breast and bilateral breast cancer.

***After Bonferroni correction, this P value is not significant.

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio; PV, pathogenic or likely pathogenic variant; WT, wildtype

eTable3: Comparison of *CHEK2* p.T476M to WT and *CHEK2* monoallelic pathogenic variants

| Characteristic | WT | | <i>CHEK2</i> monoallelic PV* | | p.T476M | | p.T476M vs. WT | | p.T476M vs. <i>CHEK2</i> PV* | |
|----------------------------------|------------|-------|------------------------------|-------|--------------|-------|------------------|-----------------|------------------------------|-----------------|
| | No. | % | No. | % | No. | % | OR (95% CI) | P value | OR (95% CI) | P value |
| Age at first breast cancer (IQR) | 50 (43-59) | | 47 (41-56) | | 49 (42-57.5) | | | 0.50 | | 0.10 |
| Age at first cancer (IQR) | 49 (42-58) | | 47 (40-56) | | 48.5 (42-57) | | | 0.44 | | 0.20 |
| Race, ethnicity and ancestry | | | | | | | | | | |
| African American/Black | 1815 | 5.5% | 37 | 1.7% | 5 | 2.0% | 0.36 (0.12-0.86) | 0.01 | 1.38 (0.42-3.59) | 0.42 |
| Ashkenazi Jewish | 2247 | 6.8% | 92 | 4.2% | 3 | 1.2% | 0.18 (0.04-0.52) | <.001 | 0.33 (0.07-1.02) | 0.06 |
| Asian | 1071 | 3.2% | 20 | 0.9% | 2 | 0.8% | 0.24 (0.03-0.9) | 0.03 | 1.02 (0.11-4.27) | >.99 |
| White | 21907 | 66.3% | 1707 | 78.7% | 167 | 66.8% | | | | |
| Hispanic | 1582 | 4.8% | 66 | 3.0% | 10 | 4.0% | 0.83 (0.39-1.57) | 0.65 | 1.55 (0.7-3.1) | 0.22 |
| Other | 4409 | 13.4% | 246 | 11.4% | 63 | 25.2% | 1.87 (1.38-2.52) | <.001 | 2.62 (1.87-3.63) | <.001 |
| Any Cancer | | | | | | | 1.11 (0.84-1.49) | 0.49 | 0.78 (0.58-1.06) | 0.10 |
| Yes | 23065 | 69.8% | 1664 | 76.8% | 180 | 72.0% | | | | |
| No | 9969 | 30.2% | 504 | 23.3% | 70 | 28.0% | | | | |
| No. of primary cancer | | | | | | | | | | |
| 0 | 9969 | 30.2% | 504 | 23.3% | 70 | 28.0% | | | | |
| 1 | 18498 | 56.0% | 1348 | 62.2% | 153 | 61.2% | | | | |
| >1 | 4567 | 13.8% | 316 | 14.6% | 27 | 10.8% | | 0.21 | | 0.11 |
| Breast cancer** | | | | | | | 1.35 (1.03-1.77) | 0.03*** | 0.74 (0.56-0.98) | 0.04*** |
| Yes | 16029 | 52.7% | 1339 | 67.1% | 139 | 59.9% | | | | |
| No | 13584 | 44.6% | 620 | 31.1% | 87 | 37.5% | | | | |
| Bilateral breast cancer** | | | | | | | 1.46 (0.95-2.23) | 0.08 | 0.73 (0.47-1.14) | 0.17 |
| Yes | 2228 | 7.3% | 273 | 13.7% | 24 | 10.3% | | | | |
| No | 27345 | 89.9% | 1683 | 84.4% | 202 | 87.1% | | | | |
| Colorectal cancer | | | | | | | 0.86 (0.49-1.41) | 0.64 | 1.38 (0.76-2.37) | 0.23 |
| Yes | 2575 | 7.8% | 109 | 5.0% | 17 | 6.8% | | | | |
| No | 29550 | 89.5% | 2015 | 92.9% | 227 | 90.8% | | | | |
| Kidney cancer | | | | | | | 1.86 (0.38-5.56) | 0.23 | 0.72 (0.14-2.31) | 0.79 |
| Yes | 214 | 0.7% | 36 | 1.7% | 3 | 1.2% | | | | |

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|-------------------|-------|-------|------|-------|-----|-------|------------------|------|------------------|------|
| No | 31896 | 96.6% | 2088 | 96.3% | 241 | 96.4% | | | | |
| Melanoma | | | | | | | 0.51 (0.16-1.22) | 0.18 | 0.72 (0.22-1.8) | 0.68 |
| Yes | 1259 | 3.8% | 60 | 2.8% | 5 | 2.0% | | | | |
| No | 30854 | 93.4% | 2064 | 95.2% | 239 | 95.6% | | | | |
| Pancreatic cancer | | | | | | | 0.66 (0.13-1.95) | 0.64 | 1.31 (0.25-4.46) | 0.73 |
| Yes | 597 | 1.8% | 20 | 0.9% | 3 | 1.2% | | | | |
| No | 31517 | 95.4% | 2104 | 97.1% | 241 | 96.4% | | | | |
| Thyroid cancer | | | | | | | 1.33 (0.53-2.8) | 0.38 | 0.82 (0.31-1.8) | 0.85 |
| Yes | 696 | 2.1% | 74 | 3.4% | 7 | 2.8% | | | | |
| No | 31416 | 95.1% | 2050 | 94.6% | 237 | 94.8% | | | | |

**CHEK2* PV – pathogenic and likely pathogenic variants in *CHEK2* excluding the lower risk *CHEK2* variants: p.I157T, p.S428F and p.T476M

**Denominator for sex-specific cancers was total number of females with given variant for breast and bilateral breast cancer.

***After Bonferroni correction, this P value is not significant.

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio; PV, pathogenic or likely pathogenic variant; WT, wildtype

eTable4: Cancer Associations by WT vs. *CHEK2* Monoallelic pathogenic variants

| Characteristic | WT | | <i>CHEK2</i> monoallelic PV* | | WT vs. <i>CHEK2</i> monoallelic PV | |
|---------------------|-------|-------|------------------------------|-------|------------------------------------|---------|
| | No. | % | No. | % | OR (95% CI) | P value |
| Adrenal cancer | | | | | 0 (0-6.75) | >.99 |
| Yes | 10 | 0.03% | 0 | 0.0% | | |
| No | 32101 | 97.2% | 2124 | 98.0% | | |
| Brain cancer | | | | | 1.39 (0.74-2.4) | 0.26 |
| Yes | 153 | 0.5% | 14 | 0.7% | | |
| No | 31957 | 96.7% | 2110 | 97.3% | | |
| Endometrial cancer* | | | | | 0.48 (0.34-0.66) | <.001 |
| Yes | 1291 | 4.2% | 42 | 2.1% | | |
| No | 28285 | 93.0% | 1914 | 95.9% | | |
| Gastric cancer | | | | | 0.81 (0.38-1.52) | 0.66 |
| Yes | 187 | 0.6% | 10 | 0.5% | | |
| No | 31925 | 96.6% | 2114 | 97.5% | | |
| Sarcoma | | | | | 0.86 (0.49-1.43) | 0.72 |
| Yes | 280 | 0.9% | 16 | 0.7% | | |
| No | 31830 | 96.4% | 2108 | 97.2% | | |
| Prostate cancer* | | | | | 1.07 (0.65-1.7) | 0.72 |
| Yes | 329 | 12.6% | 23 | 13.4% | | |
| No | 2211 | 84.9% | 144 | 83.7% | | |
| Ovarian cancer* | | | | | 0.98 (0.79-1.21) | 0.92 |
| Yes | 1521 | 5.0% | 99 | 5.0% | | |
| No | 28057 | 92.2% | 1858 | 93.1% | | |

*Denominator for sex-specific cancers was total number of females with endometrial and ovarian cancer and total number of males with prostate cancer.

Abbreviations: CI, confidence interval; OR, odds ratio; PV, pathogenic or likely pathogenic variant; WT, wildtype

eTable5: Cancer Phenotype of Individual *CHEK2* PVs: R117G, c.1100del, ex8-9del, and c.444+1G>A compared to Wildtype and Other *CHEK2* PVs

| | p.R117G | R117G vs. WT | | R117G vs. Other PV* | | c.444+1G>A | c.444+1G>A vs. WT | | c.444+1G>A vs. Other PV* | |
|-----------------------|------------------|-------------------------|----------------|--------------------------------|----------------|----------------------|-----------------------------|----------------|------------------------------------|----------------|
| | (n=125) | | | | | (n=92) | | | | |
| Characteristic | No. (%) | OR (95% CI) | P value | OR (95% CI) | P value | No. (%) | OR (95% CI) | P value | OR (95% CI) | P value |
| Adrenal cancer | 0 (0.0%) | 1 | >.99 | 1 | >.99 | 0 (0.0%) | 1 | >.99 | 1 | >.99 |
| Brain cancer | 1 (0.8%) | 1.71 (0.04-9.86) | 0.45 | 1.25 (0.03-8.48) | 0.57 | 1 (1.1%) | 2.35 (0.06-13.61) | 0.35 | 1.75 (0.04-11.87) | 0.46 |
| Endometrial cancer* | 3 (0.7%) | 0.6 (0.12-1.81) | 0.64 | 1.27 (0.25-4.11) | 0.73 | 1 (1.2%) | 0.27 (0.01-1.55) | 0.27 | 0.55 (0.01-3.34) | >.99 |
| Gastric cancer | 0 (0.0%) | 0 (0-5.25) | >.99 | 0 (0-7.31) | >.99 | 1 (1.1%) | 1.92 (0.05-11.09) | 0.41 | 2.53 (0.06-18.58) | 0.35 |
| Sarcoma | 1 (0.8%) | 0.93 (0.02-5.33) | >.99 | 1.09 (0.03-7.17) | 0.62 | 0 (0.0%) | 0 (0-4.79) | >.99 | 0 (0-5.92) | >.99 |
| Prostate cancer* | 2 (16.7%) | 1.49 (0.16-7.26) | 0.64 | 1.43 (0.14-7.6) | 0.65 | 1 (12.5%) | 0.96 (0.02-7.51) | >.99 | 0.89 (0.02-7.5) | >.99 |
| Ovarian cancer* | 5 (4.4%) | 0.86 (0.27-2.08) | >.99 | 0.87 (0.27-2.17) | >.99 | 4 (4.8%) | 0.95 (0.25-2.53) | >.99 | 0.96 (0.25-2.64) | >.99 |
| | | | | | | | | | | |
| | c.1100del | c.1100del vs. WT | | c.1100del vs. Other PV* | | Ex8-9del | Ex8-9del vs. WT | | Ex8-9del vs. Other PV* | |
| | (n=1252) | | | | | (n=113) | | | | |
| Characteristic | No. (%) | OR (95% CI) | P value | OR (95% CI) | P value | No. (%) | OR (95% CI) | P value | OR (95% CI) | P value |
| Adrenal cancer | 0 (0.0%) | 1 | >.99 | 1 | >.99 | 0 (0.0%) | 1 | >.99 | 1 | >.99 |
| Brain cancer | 8 (0.6%) | 1.38 (0.58-2.79) | 0.394 | 0.98 (0.3-3.45) | >.99 | 1 (0.9%) | 1.88 (0.05-10.86) | 0.42 | 1.39 (0.03-9.38) | 0.53 |
| Endometrial cancer* | 23 (2.0%) | 0.46 (0.29-0.69) | <.001 | 0.9 (0.46-1.76) | 0.75 | 2 (1.9%) | 0.42 (0.05-1.56) | 0.33 | 0.87 (0.1-3.44) | >.99 |
| Gastric cancer | 6 (0.5%) | 0.84 (0.3-1.87) | 0.85 | 1.11 (0.26-5.34) | >.99 | 1 (0.9%) | 1.54 (0.04-8.85) | 0.48 | 2 (0.05-14.68) | 0.42 |
| Sarcoma | 12 (1.0%) | 1.13 (0.57-2.01) | 0.64 | 2.22 (0.67-9.48) | 0.21 | 0 (0.0%) | 0 (0-3.83) | >.99 | 0 (0-4.69) | >.99 |
| Prostate cancer* | 10 (9.6%) | 0.75 (0.34-1.46) | 0.45 | 0.46 (0.17-1.23) | 0.11 | 1 (16.7%) | 1.34 (0.03-12.06) | 0.57 | 1.26 (0.03-12.07) | 0.60 |
| Ovarian cancer* | 54 (4.7%) | 0.93 (0.69-1.23) | 0.68 | 0.89 (0.58-1.36) | 0.60 | 3 (2.8%) | 0.54 (0.11-1.62) | 0.38 | 0.53 (0.11-1.65) | 0.37 |

*Denominator for sex-specific cancers was total number of females with endometrial and ovarian cancer and total number of males with prostate cancer.

Abbreviations: CI, confidence interval; OR, odds ratio; PV, pathogenic or likely pathogenic variant; WT, wildtype

eTable6: Cohort Characteristics and Cancer Associations comparing *CHEK2* Monoallelic PV versus Biallelic PV

| Characteristic | WT | | <i>CHEK2</i> monoallelic PVs* | | <i>CHEK2</i> biallelic PV* | | Biallelic PV* vs. WT | | Biallelic vs. Monoallelic PV* | |
|----------------------------------|------------|-------|-------------------------------|-------|----------------------------|-------|----------------------|-----------------|-------------------------------|-----------------|
| | No. | % | No. | % | No. | % | OR (95% CI) | P value | OR (95% CI) | P value |
| Age at first breast cancer (IQR) | 50 (43-59) | | 47 (41-56) | | 40.5 (35-48) | | | 0.001 | | 0.016 |
| Age at first cancer (IQR) | 49 (42-58) | | 47 (40-56) | | 37 (32.5-45) | | | <.001 | | <.001 |
| Race, ethnicity and ancestry | | | | | | | | | | |
| African American/Black | 1815 | 5.5% | 37 | 1.7% | 0 | 0.0% | 0 (0-2.45) | 0.40 | 0 (0-9.78) | >.99 |
| Ashkenazi Jewish | 2247 | 6.8% | 92 | 4.2% | 1 | 4.8% | 0.49 (0.01-3.05) | 0.72 | 0.93 (0.02-5.93) | >.99 |
| Asian | 1071 | 3.2% | 20 | 0.9% | 0 | 0.0% | 0 (0-4.15) | >.99 | 0 (0-18.79) | >.99 |
| White | 21907 | 66.3% | 1707 | 78.7% | 20 | 95.2% | | | | |
| Hispanic | 1582 | 4.8% | 66 | 3.0% | 0 | 0.0% | 0 (0-2.81) | 0.64 | 0 (0-5.38) | >.99 |
| Other | 4409 | 13.4% | 246 | 11.4% | 0 | 0.0% | 0 (0-1.01) | 0.04*** | 0 (0-1.42) | 0.16 |
| Any Cancer | | | | | | | 8.64 (1.38-357.8) | 0.008 | 6.05 (0.96-251.3) | 0.06 |
| Yes | 23065 | 69.8% | 1664 | 76.8% | 20 | 95.2% | | | | |
| No | 9969 | 30.2% | 504 | 23.3% | 1 | 4.8% | | | | |
| No. of primary cancer | | | | | | | | | | |
| 0 | 9969 | 30.2% | 504 | 23.3% | 1 | 4.8% | | | | |
| 1 | 18498 | 56.0% | 1348 | 62.2% | 10 | 47.6% | | | | |
| > 1 | 4567 | 13.8% | 316 | 14.6% | 10 | 47.6% | | <.001 | | <.001 |
| Breast cancer** | | | | | | | Inf (4.18-Inf) | <.001 | Inf (2.28-Inf) | <.001 |
| Yes | 16029 | 52.7% | 1339 | 67.1% | 20 | 95.2% | | | | |
| No | 13584 | 44.6% | 620 | 31.1% | 0 | 0.0% | | | | |
| Bilateral breast cancer** | | | | | | | 5.26 (1.65-14.58) | 0.003*** | 2.64 (0.82-7.39) | 0.052 |
| Yes | 2228 | 7.3% | 273 | 13.7% | 6 | 28.6% | | | | |
| No | 27345 | 89.9% | 1683 | 84.4% | 14 | 66.7% | | | | |
| Colorectal cancer | | | | | | | 1.28 (0.14-5.33) | 0.67 | 2.05 (0.23-8.75) | 0.28 |
| Yes | 2575 | 7.8% | 109 | 5.0% | 2 | 9.5% | | | | |
| No | 29550 | 89.5% | 2015 | 92.9% | 18 | 85.7% | | | | |
| Kidney cancer | | | | | | | 0 (0-30.43) | >.99 | 0 (0-12.3) | >.99 |

| | | | | | | | | | | |
|-------------------|-------|-------|------|-------|----|-------|-------------------|----------|-------------------|---------|
| Yes | 214 | 0.7% | 36 | 1.7% | 0 | 0.0% | | | | |
| No | 31896 | 96.6% | 2088 | 96.3% | 20 | 95.2% | | | | |
| Melanoma | | | | | | | 2.72 (0.31-11.4) | 0.18 | 3.82 (0.42-16.54) | 0.11 |
| Yes | 1259 | 3.8% | 60 | 2.8% | 2 | 9.5% | | | | |
| No | 30854 | 93.4% | 2064 | 95.2% | 18 | 85.7% | | | | |
| Pancreatic cancer | | | | | | | 0 (0-10.73) | >.99 | 0 (0-23.16) | >.99 |
| Yes | 597 | 1.8% | 20 | 0.9% | 0 | 0.0% | | | | |
| No | 31517 | 95.4% | 2104 | 97.1% | 20 | 95.2% | | | | |
| Thyroid cancer | | | | | | | 7.96 (1.49-27.63) | 0.009*** | 4.88 (0.9-17.42) | 0.03*** |
| Yes | 696 | 2.1% | 74 | 3.4% | 3 | 14.3% | | | | |
| No | 31416 | 95.1% | 2050 | 94.6% | 17 | 81.0% | | | | |

**CHEK2* PV – pathogenic and likely pathogenic variants in *CHEK2* excluding the lower risk *CHEK2* variants: p.I157T, p.S428F and p.T476M

**Denominator for sex-specific cancers was total number of females with given variant for breast and bilateral breast cancer.

***After Bonferroni correction, this P value is not significant.

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio; PV, pathogenic or likely pathogenic variant; WT, wildtype

eTable7: Cohort Characteristics and Cancer Associations of LOF versus missense *CHEK2* pathogenic variants.

| Characteristic | LOF | | Missense | | LOF vs. Missense | |
|--------------------------------------|------------|-------|--------------|-------|-------------------|--------------|
| | No. | % | No. | % | OR (95% CI) | P value |
| Age at first breast cancer (IQR) | 48 (41-56) | | 46.5 (40-54) | | | 0.33 |
| Age at first cancer (IQR) | 47 (40-56) | | 46 (39-54) | | | 0.26 |
| Race, ethnicity and ancestry | | | | | | |
| African American/Black | 34 | 1.8% | 3 | 1.2% | 1.38 (0.43-7.08) | 0.79 |
| Ashkenazi Jewish | 88 | 4.6% | 4 | 1.6% | 2.67 (0.99-10.15) | 0.053 |
| Asian | 16 | 0.8% | 4 | 1.6% | 0.49 (0.15-2.02) | 0.26 |
| White | 1522 | 79.1% | 185 | 75.8% | | |
| Hispanic | 50 | 2.6% | 16 | 6.6% | 0.38 (0.21-0.73) | 0.002 |
| Other | 214 | 11.1% | 32 | 13.1% | 0.81 (0.54-1.26) | 0.33 |
| Any Cancer | | | | | 1.23 (0.89-1.68) | 0.20 |
| Yes | 1485 | 77.2% | 179 | 73.4% | | |
| No | 439 | 22.8% | 65 | 26.6% | | |
| No. of primary cancer | | | | | | |
| 0 | 439 | 22.8% | 65 | 26.6% | | |
| 1 | 1198 | 62.3% | 150 | 61.5% | | |
| >1 | 287 | 14.9% | 29 | 11.9% | | 0.26 |
| Breast cancer | | | | | 1.16 (0.86-1.56) | 0.33 |
| Yes | 1195 | 67.4% | 144 | 65.2% | | |
| No | 544 | 30.7% | 76 | 34.4% | | |
| Bilateral breast cancer | | | | | 0.84 (0.57-1.24) | 0.38 |
| Yes | 238 | 13.4% | 35 | 15.8% | | |
| No | 1498 | 84.4% | 185 | 83.7% | | |
| First breast cancer ER/PR positive** | | | | | 0.69 (0.21-1.77) | 0.53 |
| Yes | 747 | 92.6% | 90 | 94.7% | | |
| No | 60 | 7.4% | 5 | 5.3% | | |
| First breast cancer HER2 positive | | | | | | |

| | | | | | | |
|-------------------|------|--------|-----|-------|------------------|------|
| Yes | 150 | 25.7% | 18 | 27.3% | 0.92 (0.51-1.74) | 0.77 |
| No | 434 | 74.3% | 48 | 72.7% | | |
| Colorectal cancer | | | | | 1.04 (0.56-2.12) | >.99 |
| Yes | 97 | 5.0% | 12 | 4.9% | | |
| No | 1785 | 92.8% | 230 | 94.3% | | |
| Kidney cancer | | | | | 1.03 (0.36-4.04) | >.99 |
| Yes | 32 | 1.7% | 4 | 1.6% | | |
| No | 1850 | 96.2% | 238 | 97.5% | | |
| Melanoma | | | | | 0.97 (0.43-2.57) | 0.84 |
| Yes | 53 | 2.8% | 7 | 2.9% | | |
| No | 1829 | 95.1% | 235 | 96.3% | | |
| Pancreatic cancer | | | | | 0.73 (0.21-3.9) | 0.49 |
| Yes | 17 | 0.9% | 3 | 1.2% | | |
| No | 1865 | 96.9% | 239 | 98.0% | | |
| Thyroid cancer | | | | | 0.93 (0.45-2.14) | 0.85 |
| Yes | 65 | 3.4% | 9 | 3.7% | | |
| No | 1817 | 94.44% | 233 | 95.5% | | |

Abbreviations: CI, confidence interval; IQR, interquartile range; LOF, loss of function; OR, odds ratio

eTable 8: Cancer Phenotype of Individual *CHEK2* PVs: R117G, c.1100del, ex8-9del, and c.444+1G>A compared to Wildtype and Other *CHEK2* PVs

| Characteristic | <u>p.R117G</u> | <u>R117G vs. WT</u> | | <u>R117G vs. Other PV*</u> | | <u>c.444+1G >A</u> | <u>c.444+1G>A vs. WT</u> | | <u>c.444+1G>A vs. Other PV*</u> | |
|----------------------------------|----------------|---------------------|-----------------------|----------------------------|-----------------------|-----------------------|-----------------------------|-----------------------|------------------------------------|-----------------------|
| | (n=125) | <i>P</i> value | <i>P</i> value | <i>P</i> value | <i>P</i> value | (n=92) | <i>P</i> value | <i>P</i> value | <i>P</i> value | <i>P</i> value |
| Age at first breast cancer (IQR) | 46.5 (41--55) | 0.03 | | 0.61 | | 50 (44-59) | 0.84 | | 0.15 | |
| Age at first cancer (IQR) | 47 (40-55) | 0.07 | | 0.70 | | 49 (44-58) | 0.88 | | 0.11 | |
| | No. (%) | OR (95% CI) | <i>P</i> value | OR (95% CI) | <i>P</i> value | No. (%) | OR (95% CI) | <i>P</i> value | OR (95% CI) | <i>P</i> value |
| Any Cancer | 91 (72.8%) | 1.16 (0.77-1.77) | 0.50 | 0.8 (0.53, 1.24) | 0.28 | 73 (79.4%) | 1.66 (0.99, 2.92) | 0.053 | 1.17 (0.69-2.08) | 0.62 |
| No. of primary cancer | | | | | | | | | | |
| 0 | 34 (27.2%) | | | | | 19 (20.7%) | | | | |
| 1 | 71 (56.8%) | | | | | 54 (58.7%) | | | | |
| >1 | 20 (16.0%) | | 0.64 | | 0.40 | 19 (20.7%) | | 0.06 | | 0.23 |
| Breast cancer** | 74 (65.6%) | 1.65 (1.12-2.44) | 0.01** * | 0.90 (0.60-1.34) | 0.59 | 62 (73.8%) | 2.63 (1.59-4.35) | < .001 | 1.46 (0.87-2.43) | 0.15 |
| Bilateral breast cancer** | 17 (15.0%) | 2.20 (1.31-3.69) | 0.002 | 1.11 (0.65-1.89) | 0.70 | 19 (22.6%) | 3.70 (2.21-6.19) | < .001 | 1.92 (1.13-3.27) | 0.01** * |
| Colorectal cancer | 5 (4.0%) | 0.49 (0.15-1.17) | 0.13 | 0.77 (0.24-1.92) | 0.83 | 4 (4.4%) | 0.53 (0.14-1.42) | 0.33 | 0.85 (0.22-2.34) | 1.0 |
| Kidney cancer | 3 (2.4%) | 3.73 (0.75-11.3) | 0.051 | 1.49 (0.29-4.86) | 0.46 | 2 (2.2%) | 3.39 (0.4-12.75) | 0.12 | 1.34 (0.15-5.36) | 0.66 |
| Melanoma | 4 (3.2%) | 0.82 (0.22-2.17) | >.99 | 1.17 (0.3-3.24) | 0.78 | 4 (4.4%) | 1.14 (0.3, 3.03) | 0.78 | 1.64 (0.42, 4.6) | 0.32 |
| Pancreatic cancer | 2 (1.6%) | 0.87 (0.1-3.23) | >.99 | 1.82 (0.2-7.75) | 0.32 4 | 0 (0.0%) | 0 (0-2.22) | 0.42 | 0 (0-4.62) | >.99 |

| | | | | | | | | | | |
|----------------|----------|------------------|--------|------------------|-------|----------|------------------|------|---------------|-----|
| Thyroid cancer | 8 (6.4%) | 3.14 (1.32-6.43) | 0.006* | 2.04 (0.83-4.39) | 0.072 | 3 (3.3%) | 1.56 (0.31-4.72) | 0.45 | 0.95 (0.19-3) | 1.0 |
|----------------|----------|------------------|--------|------------------|-------|----------|------------------|------|---------------|-----|

| Characteristic | c.1100del (n=1252) | c.1100del vs. WT | | | c.1100del vs. Other | | Ex8-9del (n=113) | Ex8-9del vs. WT | | Ex8-9del vs. Other | |
|----------------------------------|-----------------------|------------------|---------|------------------|---------------------|-------------|---------------------|-------------------|-------------|--------------------|------|
| | | OR (95% CI) | P value | OR (95% CI) | P value | OR (95% CI) | | P value | OR (95% CI) | P value | |
| Age at first breast cancer (IQR) | 48 (41-56) | | < .001 | | 0.37 | | 47.5 (40-55) | | 0.03 | | 0.72 |
| Age at first cancer (IQR) | 47 (40-56) | | < .001 | | 0.88 | | 47 (40-54.5) | | 0.06 | | 0.65 |
| Any Cancer | 956 (76.4%) | 1.4 (1.22-1.6) | < .001 | 0.95 (0.77-1.17) | 0.64 | | 91 (80.5%) | 1.79 (1.11-2.99) | 0.01 | 1.27 (0.78-2.15) | 0.36 |
| No. of primary cancer | | | | | | | | | | | |
| 0 | 296 (23.7%) | | | | | | 22 (19.5%) | | | | |
| 1 | 771 (61.6%) | | | | | | 75 (66.4%) | | | | |
| >1 | 185 (14.8%) | | < .001 | | 0.81 | | 16 (14.2%) | | 0.03 | | 0.61 |
| Breast cancer** | 760 (66.3%) | 1.76 (1.55-2.00) | < .001 | 0.92 (0.76-1.11) | 0.38 | | 78 (72.9%) | 2.36 (1.53-3.64) | < .001 | 1.31 (0.84-2.04) | 0.23 |
| Bilateral breast cancer** | 155 (13.5%) | 1.97 (1.65-2.34) | < .001 | 0.97 (0.75-1.26) | 0.83 | | 16 (15.0%) | 2.18 (1.28-3.72) | 0.003** | 1.10 (0.64-1.91) | 0.73 |
| Colorectal cancer | 69 (5.5%) | 0.69 (0.53-0.88) | 0.002 | 1.29 (0.85-1.97) | 0.23 | | 4 (3.5%) | 0.43 (0.11-1.12) | 0.11 | 0.67 (0.18-1.83) | 0.66 |
| Kidney cancer | 25 (2.0%) | 3.11 (1.96-4.74) | < .001 | 1.69 (0.8-3.82) | 0.17 | | 2 (1.8%) | 2.71 (0.32-10.14) | 0.17 | 1.06 (0.12-4.22) | 0.71 |
| Melanoma | 38 (3.0%) | 0.79 (0.55-1.09) | 0.17 | 1.28 (0.73-2.29) | 0.427 | | 3 (2.7%) | 0.67 (0.14-2.03) | 0.80 | 0.94 (0.19-2.98) | >.99 |
| Pancreatic cancer | 11 (0.9%) | 0.48 (0.24-0.87) | 0.01** | 0.9 (0.34-2.47) | 0.82 | | 1 (0.9%) | 0.48 (0.01-2.72) | 0.73 | 0.95 (0.02-6.06) | >.99 |

| | | | | | | | | | | |
|----------------|-----------|-----------------|--------------|-----------------|------|----------|------------------|------|------------------|------|
| Thyroid cancer | 44 (3.5%) | 1.68 (1.21-2.3) | 0.002 | 1.08 (0.66-1.8) | 0.81 | 4 (3.5%) | 1.67 (0.45-4.42) | 0.31 | 1.03 (0.27-2.83) | 0.80 |
|----------------|-----------|-----------------|--------------|-----------------|------|----------|------------------|------|------------------|------|

*Other PV: pathogenic and likely pathogenic variants in CHEK2 excluding the variant being compared.

**Denominator for sex-specific cancers was total number of females with given variant for breast and bilateral breast cancer.

***After Bonferroni correction, this P value is not significant.

Abbreviations: CI, confidence interval; IQR, interquartile range; OR, odds ratio; PV, pathogenic or likely pathogenic variant; WT, wildtype