**TABLE S1.**

Number and origin of families in the previous study and current study (previous plus newly included families) .

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Country** | **Previous study10** | | **Current study** | |
| **# Families** | **# Families with additional genotyping (\*)** | **# Families** | **# Families with additional genotyping (\*)** |
| **Australia** | 6 | 2 | 6 | 2 |
| **The Netherlands** | 12 | 3 | 20 | 15 |
| **Belgium** | 3 | 2 | 8 | 6 |
| **Denmark** | 10 | 4 | 22 | 19 |
| **France** | 5 | 3 | 14 | 7 |
| **Germany** | 5 | 1 | 19 | 10 |
| **South Africa** | 1 | 1 | 1 | 1 |
| **Sweden** | 14 | 5 | 20 | 17 |
| **Switzerland** | 0 | 0 | 1 | 1 |
| **United Kingdom** | 4 | 2 | 4 | 2 |
| **U.S.A.** | 9 | 7 | 14 | 11 |
| **Total** | **69** | **30** | **129** | **91** |

*(\*): additional genotyping means at least one other relative tested in addition to the index.*

**TABLE S2.**

Descriptive characteristics of the 129 families.

|  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Age** | **Unknown Carriership** | | | **Non-carriers** | | | **Carriers** | | |
| **Total** | **BC#** | **OC&** | **Total** | **BC** | **OC** | **Total** | **BC** | **OC** |
| **<30** | 2935 | 1 | 0 | 100 | 0 | 0 | 105 | 4 | 0 |
| **30-39** | 89 | 18 | 2 | 8 | 1 | 0 | 37 | 26 | 1 |
| **40-49** | 94 | 26 | 5 | 27 | 5 | 0 | 60 | 39 | 8 |
| **50-59** | 124 | 40 | 26 | 24 | 4 | 1 | 53 | 30 | 24 |
| **60-69** | 122 | 36 | 15 | 6 | 2 | 0 | 39 | 11 | 12 |
| **70-79** | 96 | 16 | 7 | 4 | 2 | 1 | 11 | 3 | 6 |
| **>=80** | 82 | 10 | 2 | 4 | 1 | 0 | 4 | 0 | 1 |
| **Total** | 3542 | 147 | 57 | 173 | 15 | 2 | 309 | 113 | 52 |

*#BC: Breast cancer*

*&OC: Ovarian cancer*

**TABLE S3.**

Cumulative risk (95% Confidence Interval) using segregation analysis, major gene models assuming constant relative risk.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Age** | **Main Analysis**  Cumulative risk  (95% Confidence Interval) | | **Sub-Analysis 1**  Cumulative risk  (95% Confidence Interval) | | **Sub-Analysis 2**  Cumulative risk  (95% Confidence Interval) | |
| **Breast**  **cancer** | **Ovarian**  **cancer** | **Breast**  **cancer** | **Ovarian**  **cancer** | **Breast**  **cancer** | **Ovarian**  **cancer** |
| **25** | 0.017  (0.010, 0.024) | 0.15  (0.06, 0.24) | 0.02  (0.01, 0.03) | 0.14  (0.04, 0.24) | 0.02  (0.01, 0.03) | 0.10  (0.03, 0.17) |
| **30** | 0.13  (0.07, 0.18) | 0.26  (0.12, 0.41) | 0.16  (0.07, 0.24) | 0.26  (0.10, 0.41) | 0.14  (0.05, 0.23) | 0.17  (0.06, 0.28) |
| **35** | 0.49  (0.31, 0.68) | 0.42  (0.21, 0.62) | 0.60  (0.32, 0.88) | 0.40  (0.17, 0.63) | 0.54  (0.23, 0.85) | 0.27  (0.11, 0.43) |
| **40** | 1.34  (0.90, 1.78) | 0.63  (0.34, 0.92) | 1.63  (0.95, 2.31) | 0.61  (0.29, 0.93) | 1.47  (0.72, 2.21) | 0.41  (0.18, 0.63) |
| **45** | 2.97  (2.08, 3.85) | 0.95  (0.52, 1.38) | 3.60  (2.23, 4.96) | 0.92  (0.45, 1.38) | 3.24  (1.74, 4.72) | 0.62  (0.29, 0.95) |
| **50** | 5.40  (3.96, 6.82) | 1.49  (0.81, 2.17) | 6.54  (4.31, 8.71) | 1.44  (0.69, 2.18) | 5.89  (3.45, 8.28) | 0.97  (0.45, 1.49) |
| **55** | 8.82  (6.68, 10.90) | 2.28  (1.25, 3.29) | 10.63  (7.36, 13.79) | 2.20  (1.08, 3.31) | 9.61  (5.99, 13.09) | 1.49  (0.70, 2.27) |
| **60** | 12.38  (9.72, 14.97) | 3.36  (1.89, 4.81) | 14.87  (10.81, 18.74) | 3.25  (1.64, 4.83) | 13.47  (8.96, 17.75) | 2.20  (1.07, 3.32) |
| **65** | 16.42  (13.23, 19.49) | 4.81  (2.78, 6.79) | 19.62  (14.80, 24.16) | 4.65  (2.42, 6.82) | 17.82  (12.43, 22.87) | 3.15  (1.58, 4.70) |
| **70** | 20.58  (16.95, 24.05) | 6.42  (3.87, 8.90) | 24.47  (19.04, 29.53) | 6.21  (3.41, 8.92) | 22.28  (16.17, 27.95) | 4.22  (2.24, 6.17) |

**TABLE S4.**

Cumulative risk (95% Confidence Interval) using segregation analysis, major gene models assuming relative risk as a continuous, piecewise linear function of age.

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| **Age** | **Main Analysis**  Cumulative risk  (95% Confidence Interval) | | **Sub-Analysis 1**  Cumulative risk  (95% Confidence Interval) | | **Sub-Analysis 2**  Cumulative risk  (95% Confidence Interval) | |
| **Breast**  **cancer** | **Ovarian**  **cancer** | **Breast**  **cancer** | **Ovarian**  **cancer** | **Breast**  **cancer** | **Ovarian**  **cancer** |
| **25** | 0.03  (0.01, 0.06) | 0.15  (0.02, 1.57) | 0.03  (0.01, 0.08) | 0.06  (3.94x10-4, 7.50) | 0.04  (0.01, 0.10) | 0.56  (0.003, 3.73) |
| **30** | 0.21  (0.10, 0.45) | 0.27  (0.03, 2.79) | 0.22  (0.08, 0.57) | 0.10  (7.01x10-4, 12.98) | 0.28  (0.08, 0.73) | 0.96  (0.005, 6.56) |
| **35** | 0.82  (0.38, 1.75) | 0.42  (0.04, 4.34) | 0.86  (0.32, 2.21) | 0.16  (1.10x10-3, 19.63) | 1.09  (0.31, 2.81) | 1.44  (0.008, 10.11) |
| **40** | 2.22  (1.04, 4.70) | 0.64  (0.06, 6.49) | 2.32  (0.87, 5.92) | 0.24  (1.66x10-3, 28.11) | 2.95  (0.85, 7.49) | 2.08  (0.01, 14.87) |
| **45** | 4.89  (2.30, 10.19) | 0.96  (0.10, 9.66) | 5.10  (1.94, 12.72) | 0.36  (2.52x10-3, 39.32) | 6.41  (1.89, 15.95) | 2.98  (0.02, 21.63) |
| **50** | 8.22  (4.22, 16.40) | 1.51  (0.30, 13.68) | 8.72  (3.86, 20.34) | 0.67  (0.12, 51.16) | 10.62  (3.69, 24.88 ) | 4.13  (0.13, 29.53) |
| **55** | 11.99  (6.82, 22.50) | 2.30  (0.66, 17.66) | 13.05  (6.73, 28.18) | 1.29  (0.36, 60.48) | 15.25  (6.06, 32.87) | 5.39  (0.34, 36.61) |
| **60** | 15.02  (9.35, 26.46) | 3.39  (1.21, 20.74) | 16.82  (9.53, 33.35) | 2.37  (0.80, 66.01) | 18.87  (8.15, 37.55) | 6.65  (0.66, 41.30) |
| **65** | 17.46  (11.37, 28.80) | 4.83  (1.99, 21.94) | 20.28  (12.18, 36.99) | 4.10  (1.51, 66.40) | 21.64  (9.93, 40.72) | 7.80  (1.14, 41.82) |
| **70** | 20.01  (13.26, 32.01) | 6.43  (2.78, 24.53) | 23.89  (14.51, 42.42) | 6.02  (2.25, 66.73) | 24.47  (11.29, 46.03) | 9.07  (1.58, 42.50) |

**TABLE S5.**

Modified segregation analysis results from MENDEL in the sub-analysis 1 and sub-analysis 2, a) assuming constant relative risk across age groups and b) assuming relative risk as a continuous, piecewise linear function of age.

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
|  | **Analysis** | **Model** | **HR (a)** | **Age** | **HR (b)** |
| Breast | Sub-Analysis 1 | Major Gene Only | 3.45 (1.88, 6.34) | < 40 | 4.93 (1.87, 12.99) |
| > 60 | 2.56 (0.96, 6.82) |
| Major and Polygenic | 4.14 (1.93, 8.91) | < 40 | 4.66 (1.53, 14.23) |
| > 60 | 3.75 (1.32, 10.72) |
| Sub-Analysis 2 | Major Gene Only | 3.10 (1.48, 6.49) | < 40 | 5.50 (1.80, 16.81) |
| > 60 | 1.59 (0.36, 7.09) |
| Major and Polygenic | 3.93 (1.56, 9.90) | < 40 | 5.07 (1.26, 20.43) |
| > 60 | 2.91 (0.47, 14.92) |
| Ovarian | Sub-Analysis 1 | Major Gene Only | 5.63 (1.86, 17.03) | < 40 | 2.18 (0.01, 337.05) |
| > 60 | 6.92 (1.80, 26.58) |
| Major and Polygenic | 5.96 (1.83, 19.44) | < 40 | 1.50 (0.01, 406.07) |
| > 60 | 7.86 (1.99, 31.09) |
| Sub-Analysis 2 | Major Gene Only | 3.79 (1.20, 11.96) | < 40 | 4.32 (0.12, 159.24) |
| > 60 | 3.68 (0.89, 15.13) |
| Major and Polygenic | 4.06 (1.99, 8.26) | < 40 | 3.48 (0.05, 259.56) |
| > 60 | 4.19 (0.95, 18.47) |

*HR: hazard ratio*