Review

Differences in Ovarian and Other Cancers Risks by Population and BRCA Mutation Location

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Abstract: Hereditary breast and ovarian cancer is caused by a germline mutation in BRCA1 or BRCA2 genes. The frequency of germline BRCA1/2 gene mutation carriers and the ratio of germline BRCA1 to BRCA2 mutations in BRCA-related cancer patients vary depending on the population. Genotype and phenotype correlations have been reported in BRCA mutant families, however, the correlations are rarely used for individual risk assessment and management. BRCA genetic testing has become a companion diagnostic for PARP inhibitors, and the number of families with germline BRCA mutation identified is growing rapidly. Therefore, it is expected that analysis of the risk of developing cancer will be possible in a large number of BRCA mutant carriers, and there is a possibility that personal and precision medicine for the carriers with specific common founder mutations will be realized. In this review, we investigated the association of ovarian cancer risk and BRCA mutation location, and differences of other BRCA-related cancer risks by BRCA1/2 mutation, and furthermore, we discussed the difference in the prevalence of germline BRCA mutation in ovarian cancer patients. As a result, although there are various discussions, there appear to be differences in ovarian cancer risk by population and BRCA mutation location. If it becomes possible to estimate the risk of developing BRCA-related cancer for each BRCA mutation type, the age at risk-reducing salpingo-oophorectomy can be determined individually. The decision would bring great benefits to young women with germline BRCA mutations.

Keywords: BRCA1/2; hereditary breast and ovarian cancer; BRCA-related cancer; risk-reducing salpingo-oophorectomy

1. Introduction

The BRCA1 gene, located on chromosome 17, and the BRCA2 gene, located on chromosome 13, are involved in the repair of double-strand DNA breaks and cell-cycle checkpoints in response to DNA damage. The functions of two genes preserve genomic stability as tumor suppressor genes [1–4]. The overall prevalence of germline mutations in BRCA1 and BRCA2 genes in unaffected women has been estimated at 0.11% and 0.24%, respectively [5]. So far, many mutations have been identified in BRCA1/2 genes. Among them, the same mutation has been found in multiple, unrelated families and can be traced back to a common ancestor. Such mutations are so-called common founder mutations observed in specific populations, e.g., 187delAG and 5385insC of BRCA1 and the 6174delT of BRCA2 in the Ashkenazi Jewish and L63X and Q934X of BRCA1 in a Japanese population [6–9]. Certain common founder mutations have also been identified in other populations [10–16]. The carriers of BRCA1/2 mutations have a high risk of specific cancer, such as breast, ovarian, pancreatic, and prostate cancer. However, the probability of cancer development in the carriers is variable, even within families with the same variant [17–19]. It is still unknown whether the risk of developing cancer in the carriers is related only to the specific mutation or whether additional genetic and environmental factors exist.
In this review article, we used three databases (PubMed, Google Scholar, and Web of Science) and references or related articles to conduct a review of the cancer risk by BRCA mutation types. We identified articles in the databases using the following search string: (“ovarian cancer” OR “breast cancer” OR “common mutation” OR “founder mutation” OR “cancer risk” OR “ethnicity” OR “race” OR “population”) AND “BRCA”. Given the search results, we added the words “Prostate cancer,” “Pancreatic cancer,” “Melanoma,” “risk-reducing salpingo-oophorectomy,” and “risk-reducing mastectomy” to cover all relevant articles.

2. Differences of the Prevalence of Germline BRCA Mutation in Ovarian Cancer Patients

2.1. Prevalence of Germline BRCA1/2 Mutation in Ovarian Cancer Patients

The risk of developing ovarian cancer is thought to increase with early menarche, delayed menopause, nulliparity, infertility, and obesity, however, the strongest risk factor for ovarian cancer is a positive family history of breast and/or ovarian cancer [20–22]. The risk of developing ovarian cancer is 2 to 6 times higher in those who have breast cancer or ovarian cancer as first-degree relatives [23–25]. Hereditary ovarian cancer occurs as part of a hereditary tumor represented by Hereditary breast and ovarian cancer (HBOC) and Lynch syndrome. Of these, HBOC is the most involved and is estimated to account for about 65–85% of hereditary ovarian cancers [26]. In large-scale epidemiologic studies, the penetrance of the BRCA1/2 gene for female breast cancer was about 70%, and there was almost no difference between BRCA1 and BRCA2 [27]. However, the penetrance of the BRCA1 or BRCA2 gene for ovarian cancer has been reported to be about 40% and 20%, respectively [27]. On the other hand, the risk of developing male breast cancer, prostate cancer, pancreatic cancer, and melanoma in BRCA2 mutation carriers has been reported to be higher than in BRCA1 [26]. Given the genetic risk of developing ovarian cancer in a population, the frequency of BRCA gene carriers in the general population leads to the direct estimation of risk factors. In addition, the frequency of germline BRCA1/2 gene mutation carriers and the ratio of germline BRCA1 to BRCA2 mutations in ovarian cancer patients may vary depending on the population.

Table 1 shows the differences in germline BRCA1/2 mutation prevalence between population and country in ovarian cancer patients [28–38]. The frequency of germline BRCA mutation ranged from 5% to 30%. Among these reports, the high frequency of germline BRCA mutation in Ashkenazi Jews stands out as already reported [22]. The frequency of germline BRCA mutation in the USA, Canada, Australia, and Japan showed average values of about 15% [29,30,35,38]. On the other hand, the frequency of germline BRCA mutation varies in European countries, but that of Finland, Sweden, Denmark and Iceland appear to be relatively low [31–33,39]. The ratio of BRCA1 to BRCA2 mutations varies from population to population, but it is consistent with previous reports that germline BRCA1 mutation was more common than germline BRCA2 mutation in ovarian cancer cases. However, reports from Iceland and Poland show that germline BRCA2 mutation was more frequent than germline BRCA1 mutation [39,40]. The exact reason for this event is unknown, but the presence and spread of common founder mutations among ethnically different populations may have affected the proportion of germline BRCA1/2 mutation.
Table 1. Differences of BRCA1/2 mutation prevalence between race and country in ovarian cancer patients.

| Country/Population     | No. of Cases | BRCA1 (%)   | BRCA2 (%)   | Ratio BRCA1:BRCA2 |
|------------------------|--------------|-------------|-------------|-------------------|
| Ashkenazi Jews [22]    | 840          | 182 (21.7%) | 64 (7.6%)   | 2.8:1             |
| USA [29]               | 1915         | 182 (9.5%)  | 98 (6.3%)   | 1.9:1             |
| Canada [30]            | 977          | 75 (7.7%)   | 54 (5.5%)   | 1.4:1             |
| Finland [31]           | 233          | 11 (4.7%)   | 2 (0.9%)    | 5.5:1             |
| Sweden [32]            | 161          | 12 (7.5%)   | 1 (0.6%)    | 12:1              |
| Denmark [33]           | 445          | 22 (4.9%)   | 4 (0.9%)    | 5.5:1             |
| Iceland [39]           | 179          | 2 (1.1%)    | 10 (5.6%)   | 1.4:1             |
| Poland [40]            | 309          | 23 (7.4%)   | 29 (9.4%)   | 0.8:1             |
| Germany [34]           | 523          | 81 (15.5%)  | 28 (5.4%)   | 2.9:1             |
| India [43]             | 239          | 37 (15.5%)  | 14 (5.9%)   | 5.5:1             |
| Turkey [42]            | 102          | 10 (9.8%)   | 7 (6.9%)    | 1.4:1             |
| Pakistan [43]          | 120          | 16 (13.3%)  | 3 (2.5%)    | 5.3:1             |
| Colombia [44]          | 100          | 13 (13.0%)  | 2 (0.2%)    | 6.5:1             |
| Australia [38]         | 809          | 70 (8.7%)   | 39 (4.8%)   | 1.8:1             |
| Japan [35]             | 634          | 63 (9.9%)   | 30 (4.7%)   | 2.1:1             |
| China [36]             | 1331         | 228 (17.1%) | 70 (5.3%)   | 3.3:1             |
| Korea [37]             | 805          | 106 (13.2%) | 51 (6.3%)   | 2.1:1             |

2.2. Histological Subtypes in BRCA-Related Ovarian Cancer

In many mutational analyses of BRCA1/2 genes for epithelial ovarian cancer, we picked up large-scale epidemiological studies of more than 500 ovarian cancer patients. Table 2 shows that the rate of germline BRCA mutation of each histological type varies by the country where the study was conducted [28–30,34–38]. Regarding high-grade serous carcinoma, the mutation rate showed a range of 16% to 28%, and the rate tended to be higher in Asian countries than in Western countries. Almost 20% of Low-grade serous carcinoma in Japan or Korea were BRCA mutated, while this was only 6% in the USA or German population. Although it is not clear due to the small number of cases, the frequency of BRCA mutation in Low-grade serous carcinoma may be lower in Asia than that in European countries. Regarding mucinous carcinoma, no case with germline BRCA mutation was found in Western countries and Japan, however, germline BRCA1/2 mutation was found in 4 of 57 cases (7.0%) in China and 1 of 18 cases (5.6%) in South Korea. There is no doubt that patients with mucinous carcinoma rarely have germline BRCA mutation [8], but it is unclear whether the involvement of BRCA gene mutations in the pathogenic mechanism of mucinous carcinoma differs between Western and Asian countries. In the histological diagnosis of ovarian cancer, the existence of a mixed type is also known, and it may be related to the diversity of pathological diagnosis rather than the molecular biological reason. Regarding endometrioid carcinoma, the mutation rate was the lowest in Japan at 6.7% and the highest in Germany and South Korea at 13.0%, but there seems to be no clear difference between the countries. There are few reports on the new classification, Seromucinous tumor of the ovary, but in the analysis of four cases in Japan and seven cases in South Korea, no case with germline BRCA1/2 mutation was found in the tumor.
Table 2. Prevalence of germline BRCA mutation by histological type in ovarian cancer patients.

| Histological Classification | USA [29] (n = 1699) | Australia [38] (n = 891) | Germany [34] (n = 462) | Japan [35] (n = 609) | China [36] (n = 1044) | Korea [37] (n = 591) |
|----------------------------|----------------------|---------------------------|------------------------|----------------------|-----------------------|----------------------|
| High-grade serous          | 16.0% (240/1498)     | 16.6% * (118/709)         | 23.2% (94/406)         | 28.5% (78/274)       | 27.2% * (229/843)    | 22.3% (95/426)       |
| Low-grade serous           | 5.7% (4/70)          | N/A *                     | 5.6% (1/18)            | 20.0% (1/5)          | N/A * (6/31)         | 19.4% (9/47)         |
| Endometrioid               | 10.9% (7/64)         | 8.4% (10/119)             | 13.0% (3/23)           | 6.7% (8/120)         | 10.8% (7/65)         | 13.0% (7/54)         |
| Clear cell                 | 6.9% (4/58)          | 6.3% (4/63)               | 0.0% (0/6)             | 2.1% (4/187)         | 7.6% (6/79)          | 7.3% (4/55)          |
| Mucinous                   | 0.0% (0/9)           | N/A                       | 0.0% (0/9)             | 0.0% (0/19)          | 7.0% (4/57)          | 5.6% (1/18)          |
| Seromucinous               | N/A                  | N/A                       | N/A (0/4)              | 0.0% (0/7)           | N/A                  | 0.0% (0/7)           |

N/A: not applicable; * including either grade.

Regarding clear cell carcinoma, Germany had the lowest rate at 0%, followed by Japan at 2.1%, and other countries at about 7%. There are significant differences between Western and East Asian countries regarding the frequency of clear cell carcinoma in all types of epithelial ovarian cancer. For example, the frequency of clear cell carcinoma in the United States is about 6%, but the frequency of clear cell carcinoma in Japan is about 25%, which is a four-fold difference [45,46]. It is known that the incidence of endometriosis is high in East Asia [47], and it is presumed that this is a factor in the higher frequency of clear cell carcinoma that develops from endometriosis than in Western countries [48]. Especially in Japan, there is a tendency that drug therapy with GnRH agonists and Dienogest is preferred over surgical therapy as a treatment for endometriosis [49], so there is a relatively high possibility that clear cell carcinoma will develop from an endometriotic cyst.

Regarding the difference between BRCA1 and BRCA2 in the frequency of histological types in each country, the frequency of serous carcinoma in cases with BRCA1 or BRCA2 mutation was about 80%, and there was almost no difference between BRCA1 and BRCA2. Among ovarian cancer patients in China and South Korea, five cases of mucinous carcinoma with BRCA1/2 mutation were found, of which three cases had a BRCA1 mutation and two cases had a BRCA2 mutation.

3. Association of Breast/Ovarian Cancer Risk and BRCA Mutation Location

Genotype and phenotype correlations have been reported in BRCA mutant families. At present, such correlations are rarely used for individual risk assessment and management. However, the data of the mutant carriers have accumulated dramatically, so the genotype and phenotype correlations may be utilized for individual risk assessment.

The ovarian cancer cluster region (OCCR) was identified in or near exon 11 in both the BRCA1 and BRCA2 genes. Mutations within the lesion increase the ratio of ovarian cancer to breast cancer, unlike variants elsewhere in both genes. The Consortium of Investigators of Modifiers of BRCA1/2 (CIMBA) revealed that the incidence of ovarian cancer is high in patients with germline BRCA mutation in the OCCR in about 30,000 BRCA mutant carriers in 33 countries around the world [50]. These results are consistent with prior reports of OCCR in BRCA1/2 genes [51–53]. On the other hand, regarding the breast cancer cluster region (BCCR), multiple regions other than exon 11 have been reported for both genes [50,54]. Rebbeck et al. speculated why OCCR is present in the BRCA1 gene as follows. Mutations in exon 11 could produce a partial BRCA1 protein encoded by the known exon 11 splice variant, while the full-length protein is lost by the process of nonsense-mediated mRNA decay (NMD). Thus, it is biologically plausible that individuals carrying mutations within exon 11 (and the OCCR) may have a different phenotype than other mutations for BRCA1 [50].
The Breast Cancer Information Core (BIC) database contains DNA sequence variations reported from around the world. The total number of database entries was 15,311 and 14,914 in \textit{BRCA1} and \textit{BRCA2}, respectively \cite{55}. Table 3 shows the top 10 pathogenic mutations in \textit{BRCA1} or \textit{BRCA2}. According to the opinion of the BIC steering committee, the sequence change of this type interferes with gene function and results in an increased risk of cancer based on available data \cite{55}. For the \textit{BRCA1} gene, the most frequently reported mutation is 185delAG, followed by 5382insC, C61G, 4184del4, R1443X, 3875del4, and exon13ins6kb. The above seven variants showed the number of entries of 100 times or more. Among these common founder mutations, the mutations located within OCCR are Q563X, 2800delAA, E1250X, and 3875del4 in \textit{BRCA1} and 4075delGT in \textit{BRCA2} (Figure 1). In a recent report, Yoshihara et al. reported that more than 50\% of Japanese ovarian cancer patients with \textit{BRCA1} or \textit{BRCA2} mutations were within the OCCR after excluding 16 cases with L63X founder mutation \cite{56}. On the other hand, Cardoso et al. reported that 33\% (20/60) of Argentine ovarian cancer patients with \textit{BRCA1} mutations were beyond the OCCR, in stark contrast with 61\% (22/36) of the patients with \textit{BRCA2} mutations being inside the OCCR \cite{57}. Moreover, Teixeira et al. reported that among Dutch \textit{BRCA1} families, ovarian cancer risks were higher in women with OCCR mutations than non-OCCR mutations, but not in \textit{BRCA2} families \cite{58}.

Rebeck et al. reported that exon 11 mutations were associated with earlier ages in breast and ovarian cancer diagnosis and mutations conferring NMD or premature termination codon were associated with a later age at breast cancer diagnosis in \textit{BRCA1}. In \textit{BRCA2}, the mean age was greater for mutations in OCCR vs. mutations not in OCCR (45.0 vs. 43.9 years, \(p < 0.001\)), lower for mutations in BCCR1 vs. mutations not in BCCR1 (42.6 vs. 44.3 years; \(p = 0.004\)), and lower for mutations in BCCR2 vs. mutations not in BCCR2 (43.5 vs. 44.3 years, \(p = 0.04\)) \cite{50}.

### Table 3. Common mutation types of \textit{BRCA1} or \textit{BRCA2} genes in the BIC database.

| BIC Designation | Number of Entries | Exon | HGVS cDNA | HGVS Protein | Mutation Type | Population         |
|-----------------|-------------------|------|-----------|--------------|---------------|-------------------|
| \textit{BRCA1}  |                   |      |           |              |               |                   |
| 185delAG        | 2038              | 2    | c.66_67delAG | p.Glu23ValfsTer17 | Frameshift    | Ashkenazi Jewish  |
| 5382insC        | 1093              | 20   | c.5263,5264insC | p.Gln1756ProfsTer74 | Frameshift    | Ashkenazi Jewish  |
| C61G            | 239               | 5    | c.181T>G   | p.Cys61Gly    | Missense      | Europe            |
| 4184del4        | 144               | 11   | c.4065_4068delITCAA | p.Asn1355LysfsTer10 | Frameshift    | Asia              |
| R1443X          | 136               | 13   | c.4237C>T  | p.Arg1443Ter  | Nonsense      | Europe            |
| 3875del4        | 124               | 11   | c.3756_3759delGTCT | p.Ser1253ArgfsTer10 | Frameshift    | Europe            |
| exon13ins6kb    | 111               | 13   | N/A       | N/A           | Frameshift    | N/A               |
| E1250X          | 98                | 11   | c.3748G>T  | p.Glu1250Ter  | Nonsense      | Europe/Americas   |
| Q563X           | 94                | 11   | c.1687C>T  | p.Gln563Ter  | Nonsense      | N/A               |
| 2800delAA       | 81                | 11   | c.2681_2682delAA | p.Lys894ThrfsTer8 | Frameshift    | Europe            |
| \textit{BRCA2}  |                   |      |           |              |               |                   |
| 6174delIT       | 1093              | 11   | c.5946_5946delIT | p.Ser1982ArgfsTer22 | Frameshift    | Ashkenazi Jewish  |
| K3326X          | 301               | 27   | c.9976A>T  | p.Lys3326Ter  | Nonsense      | N/A               |
| 3036delE        | 111               | 11   | c.2808_2811delACAA | p.Ala938ProfsTer21 | Frameshift    | Americas          |
| 6031delTT       | 95                | 10   | c.6275_6276delITTT | p.Leu2092ProfsTer7 | Frameshift    | Americas/Europe   |
| 8765delAG       | 76                | 11   | c.8537_8538delAG | p.Glu2846GlyfsTer22 | Frameshift    | Americas/Europe   |
| 2041insA        | 75                | 10   | c.1813_1814insA | p.Asp605GlufsTer2 | Frameshift    | Europe            |
| 4075delGT       | 64                | 11   | c.3847_3848delGT | p.Val1283LysfsTer2 | Frameshift    | N/A               |
| Y1894X          | 62                | 11   | c.5682C>G  | p.Tyr1894Ter  | Nonsense      | N/A               |
| 983delE         | 61                | 9    | c.755_758delACAG | p.Asp252ValfsTer24 | Frameshift    | N/A               |
| R3128X          | 50                | 25   | c.938C>T   | p.Arg3128Ter  | Nonsense      | Europe            |

N/A: not applicable.
Various common founder mutations of the BRCA gene have been reported by different populations in the world [28,59]. It has been reported that some of these mutation carriers have a different risk of developing cancer than the overall mutation carriers. For example, Satagopan et al. reported that the estimated lifetime ovarian cancer risks were 66% (95% CI, 37–100%) due to 185delAG mutation and 29% (95% CI, 16–69%) due to 5382insC mutation [60]. There is also a report that the presence of 5382insC decreased and C61G in BRCA1 increased the risk of peritoneal cancer ($p = 0.049$ vs. $p = 0.013$) in the Polish population.
who underwent risk-reducing salpingo-oophorectomy (RRSO) [61]. Ashkenazi Jewish families with the 6174delT founder mutation were more likely to have a family member with ovarian cancer (OR = 1.58; \( p = 0.002 \)) [62]. Breast cancer risks for carriers of 6174delT were lower than those of all BRCA1 carriers (43% by age 70, 95% CI, 14% to 62%; \( p = 0.007 \)) compared with all BRCA1 mutation carriers), on the other hand, the ovarian cancer risks in the carriers were somewhat higher than the average BRCA2 risks (20% vs. 11%) [63]. The corresponding ovarian cancer risks were 14% (95% CI, 2% to 24%), 33% (8% to 50%), and 20% (2% to 35%) in carriers of the 185delAG, 5382insC in BRCA1 and 6174delT mutations in BRCA2, respectively [63]. The K3326X mutation was associated with increased risk of breast cancer (OR = 1.28, 95% CI = 1.17 to 1.40) independent of additional BRCA2 mutations and demonstrated strong association with serous ovarian cancer (OR = 1.46, 95% CI = 1.2 to 1.70), but not with prostate cancer [64].

We found L63X and Q934X as Japanese common founder mutations previously [8]. The clinical characteristics (e.g., subtype and nuclear grade of resultant cancer) of breast cancer patients with L63X might differ from those in patients with other BRCA mutations, however, the elevation of ovarian or breast cancer risk was not detected [65]. After excluding L63X founder mutation, the proportion of patients with a family history of ovarian cancer and germline BRCA1 mutations outside the OCCR was lower and the proportion of patients with a family history of breast cancer and germline BRCA1 mutations within the OCCR was relatively lower [56]. There are, relatively, many reports that BRCA carriers with common founder mutations have different risks of developing breast and ovarian cancer compared with the overall BRCA1/2 mutation, however, the results of only a few common founder mutations have been validated by multiple studies. Since the frequency of specific common founder mutations in each population varies, so does the number of breast and ovarian cancer patients who carry the mutation. In other words, 185delAG in the Ashkenazi Jewish population can be analyzed in many breast and ovarian cancer cases, so it is possible to analyze the risk of developing cancer relatively easily. However, sufficient statistical power is often not obtained in the analysis of other common founder mutations. BRCA genetic testing has become a companion diagnostic for PARP inhibitors, and the number of families with germline BRCA mutation identified is growing rapidly [66]. Therefore, it is expected that analysis of the risk of developing cancer will be possible in a large number of mutant carriers, and there is a possibility that personal and precision medicine for carriers with specific common founder mutations will be realized [67].

4. Differences of other BRCA-Related Cancers Risks by BRCA1/2 Mutation

4.1. Contralateral Breast Cancer Risk

Ten-year cumulative contralateral Breast Cancer (CBC) risks were 21.1% for BRCA1, 10.8% for BRCA2 mutation carriers and 5.1% for non-carriers [68]. On the other hand, the 15-year actuarial risk of CBC was 36.1% for BRCA1 carriers and was 28.5% for BRCA2 carriers [69]. The average cumulative risks by age 70 years for BRCA1 and BRCA2 carriers were estimated to be 83% and 62% for CBC [70,71].

4.2. Male Breast Cancer

Tai et al. reported that the cumulative risks of male breast cancer were higher in both BRCA1 and BRCA2 carriers than in non-carriers at all ages. The relative risks of developing breast cancer were highest for men in their 30s and 40s. Both the relative and cumulative risks were higher for BRCA2 carriers than for BRCA1 carriers. The estimated cumulative risk of breast carcinoma for male BRCA1 mutation carriers at age 70 years was 1.2% and for BRCA2 mutation carriers, 6.8% [72]. In addition, both retrospective and prospective analyses confirmed that breast cancer risk in men was 7.1% by age 70 years and 8.4% by age 80 years in BRCA2 carriers [71,73]. Struwing et al. reported that four (3.6%) and fifteen (13.6%) of 110 Israeli Jewish male breast cancer patients carried the BRCA1 185delAG and BRCA2 6174delT founder mutation, respectively, but not BRCA1
5382insC [74]. Lubinski et al. reported that a high risk of male breast cancer was observed with the BRCA2 6503delTT mutation (OR = 15.7; \( p = 0.023 \)) [62].

### 4.3. Prostate Cancer

Based on previously estimated population frequencies of BRCA1 and BRCA2 mutations, it was estimated that BRCA1 mutations confer a relative risk of prostate cancer of approximately 3.7-fold and 8.6-fold, which translates to an 8.6% and 15% cumulative risk by age 65 years [71,75,76]. A recent meta-analysis revealed that the relative risk of prostate cancer is 1.35-fold and 2.64-fold in BRCA1 and BRCA2 carriers, respectively. Overall survival was significantly worse among germline BRCA2 carriers compared to non-carriers [77]. BRCA2-related prostate cancer has been associated with a higher histologic grade and results in a poorer overall survival [78,79]. It was reported that BRCA2, in particular, confers a more aggressive phenotype with a higher probability of locally advanced and metastatic disease, and should be considered a prognostic marker associated with poorer survival [80]. Agalliu et al. reported that BRCA2 mutation confers a 3-fold elevated risk of high-grade prostate cancer. Although BRCA1 mutations were not associated with prostate cancer, the BRCA1 185delAG was associated with high Gleason score tumors [81].

### 4.4. Pancreatic Cancer

Several studies reported that BRCA2 carriers had higher relative and cumulative risks of pancreatic cancer compared to BRCA1 carriers [71,82,83]. Recently, Mocci et al. reported that BRCA1 carriers were at increased risk of pancreatic cancer [standardized incidence ratios (SIR) = 4.11] as were BRCA2 carriers (SIR = 5.79) in a retrospective cohort analysis [84]. A prospective study of 5,149 females with BRCA1 or BRCA2 carriers showed a significant 2.4-fold increase in the incidence of pancreatic cancer and the increase in the incidence of pancreatic cancer was similar for BRCA1 (SIR = 2.55) and BRCA2 (SIR = 2.13) [85]. Among unselected pancreatic cancer patient cohorts, multiple studies have shown to estimate the incidence of germline BRCA mutations ranged from 0.7–5.7% for BRCA2 and 0.3–2.3% for BRCA1 [86]. Of the 145 Jewish pancreatic adenocarcinoma patients, 8 patients (5.5%) were found to have BRCA mutations, 6 patients (4.1%) carried a BRCA2 mutation (6174delT) and 2 patients (1.3%) carried a BRCA1 mutation (185delAG and 5382insC) [87].

### 4.5. Melanoma

A few studies suggest that melanoma risk, both cutaneous and ocular, may be elevated in some families with BRCA2 carriers [71,88]. Moran et al. reported that an increased risk for ocular melanoma in BRCA2 carriers in 490 BRCA-mutated families [89].

### 4.6. Endometrial Cancer

Previous studies suggested that endometrial serous adenocarcinoma is not BRCA-related cancer and is more associated with tamoxifen exposure than with the effects of germline BRCA mutations [90,91]. Recently, in a prospective cohort study of BRCA carriers who received only RRSO, not hysterectomy, endometrial cancer developed in eight patients in a median follow-up of 5.1 years, with no apparent increased risk after RRSO, on the other hand, BRCA1 carriers had an increased risk of endometrial serous adenocarcinoma [92]. Furthermore, a large Dutch nationwide cohort study revealed that BRCA1/2 carriers have a 2- to 3-fold increased risk for endometrial cancer, with the highest risk observed for the rare subgroups of serous-like and p53-abnormal endometrial cancer in BRCA1 carriers [93].

### 5. Conclusions

Although there are various discussions, there appear to be differences in ovarian cancer risk by ethnicity and BRCA mutation types. These mutation-specific risks coincide with known or hypothesized functional domains and provide a basis around which accurate risk estimates can be generated for women who have inherited a particular BRCA1/2 mutation. While RRSo is certain to reduce the risk of ovarian cancer, there are some concerns about
reducing the risk of breast cancer. In a prospective cohort study, Kauff et al. reported that RRSO did not significantly reduce the breast cancer risk in BRCA1 carriers [94]. However, the latest meta-analysis has shown a significant reduction in breast cancer risk and overall mortality rate, regardless of the past history of breast cancer [95]. The risk of breast cancer does not appear to be different between BRCA1 and BRCA2 carriers [95].

The National Comprehensive Cancer Network (NCCN) guidelines state that the age at RRSO should be based on the earlier age at diagnosis of ovarian cancer patients in the family [26]. If it becomes possible to estimate the risk of developing breast and ovarian cancer and the age of onset disease for each BRCA mutation type, the age at RRSO can be determined individually. Solsky et al. reported that for BRCA1/2 carriers who delayed RRSO or who were identified with a mutation later in life, the OCCR mutation tended to be associated with lower life expectancy estimates than the BCCR and non-BCCR/OCCR mutations, so BRCA1/2 cluster regions may provide more precise estimates of life expectancy in counseling and shared decision-making [54]. The decision would bring great benefits to young women with BRCA mutations, so we hope that a lot of verifiable research will be undertaken.

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