Review

Contralateral Prophylactic Mastectomy in Women with Unilateral Breast Cancer Who Are Genetic Carriers, Have a Strong Family History or Are Just Young at Presentation

Victoria Teoh *, Marios-Konstantinos Tasoulis and Gerald Gui

Department of Breast Surgery, Royal Marsden NHS Foundation Trust, Fulham Road, London SW36JJ, UK; marios.tasoulis@rmh.nhs.uk (M.-K.T.); Gerald.Gui@rmh.nhs.uk (G.G.)
* Correspondence: victoriateoh@doctors.org.uk

Received: 27 November 2019; Accepted: 20 December 2019; Published: 6 January 2020

Abstract: The uptake of contralateral prophylactic mastectomy is rising with increasing trends that are possibly highest in the USA. Whilst its role is generally accepted in carriers of recognized high-risk predisposition genes such as BRCA1 and BRCA2 when the affected individual is premenopausal, controversy surrounds the benefit in less understood risk-profile clinical scenarios. This comprehensive review explores the current evidence underpinning the role of contralateral prophylactic mastectomy and its impact on contralateral breast cancer risk and survival in three distinct at-risk groups affected by unilateral breast cancer: known genetic carriers, those with strong familial risk but no demonstrable genetic mutation and women who are of young age at presentation. The review supports the role of contralateral prophylactic mastectomy in “high risk” groups where the evidence suggests a reduction in contralateral breast cancer risk. However, this benefit is less evident in women who are just young at presentation or those who have strong family history but no demonstrable genetic mutation. A multidisciplinary and personalized approach to support individuals in a shared-decision making process is recommended.

Keywords: contralateral prophylactic mastectomy; contralateral breast cancer; BRCA; CHEK2; PALB2; ATM; mutation carriers; family history; survival

1. Introduction

The incidence of women with breast cancer who elect to undergo contralateral prophylactic mastectomy is steadily increasing, with preponderance amongst Caucasians, young women, and those with a higher socioeconomic status [1,2]. A study of 496,488 women with unilateral Stage I–III breast cancer, from the Surveillance, Epidemiology, End Results (SEER) Program database demonstrated an increase in contralateral prophylactic mastectomy rates performed for unilateral invasive breast cancer from 3.9% in 2002 to 12.7% in 2012 [3]. This effect was reproduced in a National Cancer Database review of 553,593 patients, showing an increase in contralateral prophylactic mastectomies from 4.1% in 2003 to 9.7% in 2010. This finding was most marked in young women, where those <45 years (n = 73,888) showed an increase from 9.3% in 2003 to 26.4% in 2010 [4].

Factors that contribute to this decision include patient age, disease stage, previous breast biopsies, genetic predisposition or family history of breast cancer, fear of recurrence, concern with cosmetic symmetry and physician recommendation [1,5–8].

Patients tend to overestimate their risk of developing a contralateral breast cancer [9,10] as well as the extent of risk reduction conferred by contralateral prophylactic mastectomy [9,11]. Interestingly,
whilst 43.9% of women with breast cancer considered contralateral prophylactic mastectomy, only 38.1% were aware that it did not improve survival, highlighting the importance of patient education [12].

Improvements in modern multidisciplinary management have led to a reduction in the incidence of contralateral breast cancer from approximately 0.6% to 0.2–0.5%/year [13]. Consequently, the role of contralateral prophylactic mastectomy and the context in which it is supported is debatable.

This comprehensive review explores the current evidence underpinning the role of contralateral prophylactic mastectomy and its impact on contralateral breast cancer risk and survival in three high-risk groups affected by breast cancer: (i) genetic carriers, (ii) strong family history with no demonstrable mutation, and (iii) young women.

2. Methods

A comprehensive literature review was performed, assessing all studies published in the English literature from 1974 to March 2019 across Embase and Medline search engines. Search terms “contralateral prophylactic mastectomy”, “unilateral breast cancer”, “BRCA”, “TP53”, “PALB2”, “CHEK2”, “ATM”, “mutation carrier”, “family history”, “young women”, “non-genetic carriers”, “overall survival”, “disease-free survival”, “contralateral breast cancer” and “risk” were included. Relevant references from identified papers were also included.

3. BRCA 1/2 Carriers with Breast Cancer

3.1. BRCA 1/2 Carriers and Contralateral Breast Cancer Risk

BRCA carriers with breast cancer carry a higher risk of contralateral breast cancer, 23.7% (95% CI 17.6–30.5), compared with non-carriers, 6.8% (95% CI 4.2–10), respectively, (RR 3.56, 95% CI 2.50–5.08; \( p < 0.001 \)). This risk was higher in BRCA1 compared to BRCA2 carriers (RR 1.42, 95% CI 1.01–1.99; \( p = 0.04 \)) [14]. In a Dutch multicentre study of 6294 invasive breast cancer patients ≤50 years, the risk of contralateral breast cancer for BRCA1/2 carriers at a median follow-up of 12.5 years was shown to be 2–3 times higher compared to non-carriers (HR 3.31, 95% CI 2.41–4.55; \( p < 0.001 \) and 2.17, 95% CI 1.22–3.85; \( p = 0.01 \) respectively). The 10-year cumulative contralateral breast cancer risk following the initial breast cancer diagnosis was 21.1% for BRCA1, 10.8% for BRCA2 and 5.1% for non-carriers [15]. These findings were confirmed in a recent multicentre study where the 10-year cumulative risk was 25.1% (95% CI 19.6–31.9) for BRCA1, 13.5% (95% CI 9.2–19.1) for BRCA2 and 3.6% (95% CI 2.2–5.7) for non-carriers [16].

The age of first breast cancer diagnosis is a significant predictor of contralateral breast cancer risk in BRCA carriers [17–19]. Risk estimates vary in the literature, ranging from 23.7–30.7% in young women (<40 years) across BRCA1/2 carriers combined (BRCA1: 24–32%; BRCA2: 17–29%) [19–24]. This risk is lower in the >40 years age group, ranging from 8.4–21% (BRCA1: 11–52%; BRCA2: 7–18%) [15,17,19–22,24,25]. Similar results were shown in another study demonstrating a 10-year cumulative contralateral breast cancer risk of 23.9% (BRCA1: 25.5%; BRCA2: 17.2%) in patients <41 years, compared to 12.6% in the 41–49 year group (BRCA1 15.6%; BRCA2 7.2%) [15].

In a retrospective study of 1042 BRCA1/2 carriers with breast cancer, Graeser demonstrated that the 25-year cumulative contralateral breast cancer risk for BRCA1 carriers with the first breast cancer diagnosis at age <40 years, 40–50 years and >50 years, was 62.9% (95% CI 50.4–75.4), 43.7% (95% CI 24.9–62.5) and 19.6% (95% CI 5.3–33.9) respectively. In BRCA2 carriers, the corresponding rates were 63% (95% CI 32.8–93.2), 48.8% (95% CI 22.7–74.9) and 16.7% (95% CI 1.0–32.4) for the respective age groups [19].

3.2. Contralateral Prophylactic Mastectomy and Risk of Contralateral Breast Cancer

Contralateral prophylactic mastectomy reduces the risk of contralateral breast cancer in BRCA mutation carriers [14,26,27]. This risk reduction has been reported to be in the range of 91% [27]. This
is further supported by a meta-analysis showing that contralateral prophylactic mastectomy resulted in a 93% reduction in contralateral breast cancer risk (RR 0.072; 95% CI 0.035–0.588) [26].

3.3. Contralateral Prophylactic Mastectomy and Survival

There is conflicting evidence on whether contralateral prophylactic mastectomy improves survival in BRCA carriers with breast cancer [14,26–31] (Table 1). In a multicenter, retrospective study of 242 BRCA carriers with breast cancer, contralateral prophylactic mastectomy was associated with improved overall survival on multivariate analysis, having adjusted for risk-reducing salpingo-oophorectomy (HR 0.49, 95% CI 0.29–0.82) [30]. Similar findings have been reported in other cohort studies [27,29–31].

Table 1. Studies looking at the impact of CPM on CBC risk and survival in BRCA1/2 mutation carriers.

| Author          | Year | Study Type       | Follow up | Patient | Findings                                                                 |
|-----------------|------|------------------|-----------|---------|--------------------------------------------------------------------------|
| Li [26]         | 2016 | Meta-analysis    | n/a       | 4/4574  | CPM significantly decreased CBC risk in BRCA1/2 mutation carriers (RR 0.072; 95% CI 0.035–0.148). CPM is associated with a decrease in “all-cause” mortality (HR 0.512; 95% CI 0.368–0.588) |
| Valachis [14]   | 2014 | Meta-analysis    | n/a       | 2/13    | CPM was not associated with a benefit in BCSS HR 0.78 (95% CI 0.44–1.39, p = 0.40) |
| Copson [32]     | 2018 | Prospective cohort | Median 8.2 years | 21 BRCA carriers/10 non-carriers, with TNBC | CPM conferred no difference in 5-year OS between BRCA carriers and non-carriers with TNBC 83% (95% CI 74–89) vs. 74% (95% CI 69–78) HR 0.98 (95% CI 0.58–1.65), p = 0.94 |
| Heemskerk-Gerritsen [30] | 2015 | Multicentre retrospective cohort | Median 11.4 years | 242/583 (52%) carriers with BC who underwent CPM | CPM improved OS HR 0.49 (0.29–0.82) |
| Metcalfe [29]   | 2014 | Retrospective observational | Median follow up 14.3 yrs (0.1–20.0) | 390 BRCA1/BRCA2 carriers with a positive family history | At 20 years follow up, CPM was associated with a 48% reduction in death from breast cancer (HR 0.52; p = 0.03). * Not significant on propensity score adjusted analysis |
| Evans [31]      | 2013 | Retrospective case-control | Median 9.7 years | 105/698 (15%) BRCA 1/2 carriers with BC who underwent CPM | CPM improves OS 89% (CPM) vs. 71% (non-CPM) at 10 year follow up (p < 0.001) |
| Van Sprundel [27] | 2005 | Retrospective cohort | Mean 3.5 years | 69/148 (47%) BRCA 1/2 carriers with BC who underwent CPM | CPM reduced the risk of CBC in BRCA1/2 carriers by 91% No significant difference in OS between CPM and non-CPM group HR 0.35, p = 0.14 (adjusted for prophylactic oophorectomy) |
| Brekelmans [28] | 2007 | Retrospective case-control | Median 4.3 years | 260 BRCA 1/2 carriers with BC vs. 799 non-carriers | CPM conferred no difference in BCSS HR 0.98 (95% CI 0.5–0.91, p = 0.96) |

RC: retrospective cohort; RCC: Retrospective case-control; PC: prospective cohort; BCCS: breast-cancer-specific; OS overall survival; CPM: contralateral prophylactic mastectomy; BC: breast cancer; CBC: contralateral breast cancer; TNBC: triple negative breast cancer; HR: hazard ratio.

In a retrospective study by Van Sprundel, contralateral prophylactic mastectomy was associated with superior overall survival compared to active surveillance at 5-year follow up (94% vs 77%, p = 0.03). However, this difference was not significant once adjusted for prophylactic oophorectomy (HR 0.35, p = 0.14) [27]. Notably, Metcalfe observed a survival benefit only in the second decade of follow-up following initial breast cancer diagnosis (HR 0.52, 95% CI 0.29–0.93) but not during the first 10 years of follow-up (HR 0.65, 95% CI 0.34–1.22) [29]. A meta-analysis by Valachis demonstrated no difference in breast-cancer-specific survival between BRCA carriers who underwent contralateral prophylactic mastectomy against those who did not (HR
0.78, 95% CI 0.44–1.39; \( p = 0.40 \) [14]. However, a meta-analysis including two additional studies demonstrated a decrease in “all-cause” mortality [26]. To further add to the ambiguity, a recent prospective study showed that contralateral prophylactic mastectomy conferred no benefit in 5-year overall survival between BRCA carriers and non-carriers with triple negative breast cancer [32]. The available findings should be interpreted with caution as they are mostly based on retrospective studies that may contain recognized and unrecognized biases.

4. “Other” Genetic Carriers (CHEK2, TP53, ATM, PALB2, PTEN, CDH1) with Breast Cancer

Mutations in CHEK2, TP53, ATM, PALB2, PTEN, and CDH1 account for a small fraction of familial breast cancers. The available studies are sparse and primarily family-based, with potential ascertainment bias. It should be noted that the existing literature focuses mainly on relative rather than absolute risk estimates.

4.1. “Other” Genetic Carriers and Contralateral Breast Cancer Risk

4.1.1. CHEK2 Mutation Carriers and Contralateral Breast Cancer Risk

In a recent meta-analysis, Akdeniz demonstrated an increased contralateral breast cancer risk for CHEK2*1100delC carriers (RR 2.75, 95% CI 1.77–4.27) [33]. This mutation is associated with bilateral disease and an increased risk of bilateral breast cancer which varies between two to six-fold [15,34–40] (Table 2). It has been suggested that CHEK2 carriers may be more sensitive to ionizing radiation that may contribute to contralateral breast cancer rates in patients receiving adjuvant radiotherapy following breast conserving surgery [40,41]. The true impact of radiation in this context is questionable as consistently increased contralateral breast cancer risk has been demonstrated in patients treated with or without radiotherapy (HR 4.12, 95% CI 2.49–6.83 and HR 3.17, 95% CI 1.36–7.35, respectively) [39,41].

4.1.2. TP53 Mutation Carriers and Contralateral Breast Cancer Risk

There are no studies estimating contralateral breast cancer risk in TP53 carriers with breast cancer.

4.1.3. ATM Mutation Carriers and Contralateral Breast Cancer Risk

In a multicentre, population-based, case-control study, Concannon suggested that four common variants of ATM (c.1899-55T>G; c.3161C>G; c.6348-54T>C and c.5558A>T) were associated with a lower contralateral breast cancer risk (overall RR 0.8, 95% CI 0.6–0.9) compared to those with rare, missense ATM mutations. The protective mechanisms may occur through an alteration in ATM activity as an initiator of DNA damage response or through its role in TP53 regulation [42]. Bernstein suggested that common ATM variants may exert a protective effect and reduce contralateral breast cancer risk, while rare ATM missense, deleterious variants may act synergistically with radiation exposure to increase this risk [43]. In this study, the variants: c.1899-55T>G (RR 0.5, 95% CI 0.3–0.8), c.3161C>G (RR 0.5, 95% CI 0.3–0.9), c.5558A>T (RR 0.2, 95% CI 0.1–0.6), and c.6348-54T>C (RR 0.2, 95% CI 0.1–0.8) were associated with significantly reduced risk. On the other hand, female carriers of any rare missense ATM variant, who received radiation therapy for their first breast cancer, had a significantly elevated contralateral breast cancer risk compared to unexposed women (RR = 2.8 for <1.0 Gy dose and RR = 3.3 for ≥1.0 Gy dose to the contralateral breast).

The direct relationship between the presence of ATM variants and the overall risk of contralateral breast cancer remains controversial, although the combination of radiotherapy and certain ATM missense variants appears to accelerate tumour development [44].
### Table 2. Studies looking at CBC risk and survival in CHEK2* 1100delC mutation carriers.

| Author         | Year | Study                          | Median Follow up | N            | Findings                                                                 |
|----------------|------|--------------------------------|------------------|--------------|---------------------------------------------------------------------------|
| Akdeniz [33]   | 2019 | Meta-analysis                   | N/A              | 68 studies   | CBC risk by mutation carriers<br>BRCA1 RR 3.7 (95% CI, 2.8–4.9)<br>BRCA2 RR 2.8 (95% CI, 1.8–4.3)<br>CHEK2* 1100delC RR 2.7 (95% CI, 2.0–3.7) |
| Kriege [39]    | 2014 | Retrospective, multicentre cohort study | 6.8 years        | 193/4722 (4.1%) BC patients with CHEK2* 1100delC mutation | Higher risk of CBC<br>HR 3.97 (95% CI 2.59–6.07)<br>10-year risk of CBC is 28.9% |
| Weischer [37]  | 2012 | Meta-analysis                   | 6 years          | 459/25571 (1.8%) BC patients with CHEK2* 1100delC mutation | 20-year cumulative risk of developing BC is 25–30% (HR 3.52)<br>No comment on CBC rates |
| Mellemkjaer [40]| 2008 | Population based, multicentre cohort study | N/A              | 17/2103 (0.8%) BC patients with CHEK2* 1100delC mutation | No significant association between CHEK2* 1100delC mutation and CBC |
| Breks [41]     | 2004 | Case study                      | N/A              | 15/233 (6.4%) CHEK2* 1100delC mutation carriers with BBC 2/191 (1%) CHEK2* 1100delC mutation carriers with UBC | Increased risk of CBC in carriers<br>OR 6.5 (95% CI 1.5–28.8, p = 0.005) |
| Schmidt [36]   | 2007 | Retrospective cohort study      | Median 10.1 years | 54/1479 (3.7%) pre-menopausal BC patients with CHEK2* 1100delC mutation | CHEK2* 1100delC mutation carriers:<br>Increased risk of ipsilateral second breast cancer HR 2.1 (95% CI 1.0–4.3; p = 0.049)<br>Worse breast-cancer-specific survival HR 1.4 (95% CI 1.0–2.1; p = 0.072)<br>Worse recurrence-free survival HR 1.7 (95% CI 1.2–2.4; p = 0.06) |
| De Bock [45]   | 2004 | Prospective cohort              | Median 3.8 years  | 34 BC patients with CHEK2* 1100delC mutation; 102 BC patients with no mutation | Compared to non-carriers, CHEK2* 1100delC mutation carriers:<br>Increased risk of CBC compared<br>RR = 5.74 (95% CI 1.67–19.65)<br>Increased risk of distant metastasis<br>RR 2.81 (95% CI 1.2–6.58)<br>Worse DFS<br>RR = 3.86 (1.91–7.78)<br>No difference in overall survival. Mutation carriers more frequently had a 1st or 2nd degree female relative with breast cancer (p = 0.03) |

BC: breast cancer; CBC: contralateral breast cancer; BBC: bilateral breast cancer; UBC: unilateral breast cancer; RR: relative risk; DFS: disease-free survival; ER: oestrogen receptor; HR: hazard ratio.

### 4.1.4. PALB2 Mutation Carriers and Contralateral Breast Cancer Risk

There are no studies estimating contralateral breast cancer risk in PALB2 carriers with breast cancer.

### 4.1.5. CDH1 Mutation Carriers and Contralateral Breast Cancer Risk

There are no studies on the risk of contralateral breast cancer in CDH1 carriers.

### 4.1.6. PTEN Mutation Carriers and Contralateral Breast Cancer Risk

There are no studies estimating contralateral breast cancer risk in PTEN carriers with breast cancer.
4.2. Contralateral Prophylactic Mastectomy and Risk of Contralateral Breast Cancer

No studies have investigated the role of contralateral prophylactic mastectomy in the risk reduction of contralateral breast cancer in patients with a diagnosis of breast cancer that harbor a genetic mutation in non-BRCA1/2 genes (CHEK2, TP53, ATM, PALB2, CDH1 and PTEN).

4.3. Contralateral Prophylactic Mastectomy and Survival

There is no data to support any survival benefit from contralateral prophylactic mastectomy in this group of patients (“other” genetic carriers). This would be even more challenging in those with TP53, CDH1 and PTEN mutations because of the additional competing cancer risk. In view of the limited evidence, no further comment can be made, except to reinforce that contralateral prophylactic mastectomy should be considered on an individual basis for women with unilateral breast cancer in this group.

5. Familial Breast Cancers with no Demonstrable Genetic Mutations

5.1. Familial Breast Cancers with No Demonstrable Genetic Mutation and Contralateral Breast Cancer Risk

A positive family history remains a strong risk factor for contralateral breast cancer, even after excluding mutation carriers [46–48]. Table 3 summarizes the current literature on the impact of positive family history on contralateral breast cancer risk and survival. In a multicentre, population-based, case-control study of 1521 contralateral breast cancer cases against 2212 matched controls of unilateral breast cancer, Reiner demonstrated that non-mutation carriers with any 1st or 2nd degree relative of breast cancer had a nearly two-fold increased contralateral breast cancer risk (RR 1.8, 95% CI 1.3–2.4), compared to individuals without a family history. This risk is similar to that shown in previous studies [49,50]. In this non-mutation carrier group, a 1st degree family history of bilateral breast cancer increased the contralateral breast cancer risk by more than three-fold (RR 3.4, 95% CI 1.5–7.4). Where there is only an affected 2nd degree relative, the individual is at a 40% increased risk compared to an individual without a family history. The 10-year absolute contralateral breast cancer risk in non-mutation carriers with a 1st or 2nd degree family history is 8.3% (95% CI 5.5–12.6) and 6.6% (95% CI 4.4–10) respectively [46].
### Table 3. Studies looking at the impact of positive FH of breast cancer on CBC rates, disease-free and overall survival.

| Author     | Year | Study Type                          | Follow up                  | Patients                  | Findings                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
|------------|------|-------------------------------------|----------------------------|---------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Reiner     | 2018 | Multicentre, population-based, case-control study | Not stated | 1521 CBC cases with 2212 UBC controls | A 1st degree relative with BC confers increased risk of CBC (RR 1.9 (95% CI 1.6–2.3))<br>A 1st degree relative with BBC confers the highest risk of CBC (RR 3.4 (95% CI 2.4–5))<br>A 2nd degree relative increases the risk of CBC (RR 1.4 (95% CI 1.2–1.7))<br>Any 1st degree relative with breast cancer confers a 10-year AR of developing CBC of 8.1% (95% CI 6.7–9.8).<br>The 10-year AR increases to 13.5% (95% CI 8.8–20.8) if this relative was <40 years at age of diagnosis.<br>The 10-year AR is highest at 36% (95% CI 14.5–90.5) if the first degree relative was diagnosed with BBC at age <40 years.<br>On subgroup analysis and exclusion of mutation carriers i.e., BRCA1, ATM, PALB2 and CHEK2, the increased 10-year AR associated with a 1st degree relative and a 1st degree relative with BBC remained significant similar to above-reported. |
| Kuchenbaecker | 2017 | Prospective, multicentre, cohort study | Median 4 years (2–7) | 3886 eligible for breast cancer analysis | Increased risk if ≥two 1st or 2nd degree relatives with breast cancer compared to no family history of BC; HR 1.99<br>Did not evaluate the effect of FH on CBC risk |
| Bernstein  | 1992 | Prospective cohort study            | Mean 52 months         | 136/4550 (2.9%) patients with CBC and varying familial risk | Compared with no FH of breast cancer: Increased risk of CBC ~2x with a 1st degree relative with BC<br>Increased risk of CBC ~3x if 1st degree relative was diagnosed at a young age (<35 years) |
| Ji         | 2007 | Population based, national database study | Not stated | 56190 invasive and 6841 in situ BC patients | The risk of metachronous CBC measured by SIRs was higher with primary in situ disease compared to invasive cancer.<br>SIR for metachronous CBC in women diagnosed with invasive BC: <45 years: 5.12 (95% CI 4.47–5.85)<br>45–55 years: 1.95 (95% CI 1.76–2.16)<br>55 years: 1.49 (95% CI 1.37–1.61)<br>SIR for metachronous CBC in women diagnosed with 1st invasive BC and have:<br>A positive FH 2.74 (95% CI 2.3–3.23)<br>No FH 1.85 (95% CI 1.75–1.96)<br>SIR for metachronous CBC in women diagnosed with in situ disease: <45 years: 5.12 (95% CI 4.47–5.85)<br>45–55 years: 1.95 (95% CI 1.76–2.16)<br>55 years: 1.49 (95% CI 1.37–1.61) |
### Table 3. Cont.

| Author       | Year | Study Type               | Follow up       | Patients                                                                 | Findings                                                                                                                                                                                                                                                                 |
|--------------|------|--------------------------|-----------------|---------------------------------------------------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Narod [53]   | 2016 | Population based, national database study | Not stated      | 4839 CBC patients out of 84819 patients with BC * (5.7%)                  | Young age at 1st BC diagnosis and a maternal cancer history increases the risk of CBC. The 15-year cumulative risk of CBC was: 8.8% (95% CI 8.5–9.1) in the general population (regardless of maternal BC status) 12% (95% CI 11–13) in maternal UBC 13% (95% CI 9.5–17) in maternal BBC A maternal cancer history of UBC at an early age conferred the daughter a lifetime CBC risk of 35% (95% CI 25–46) * Mutation carriers not excluded as information not available from cancer registry |
| Vaittinen [54] | 2000 | Population based, national database study | Not stated      | 2529/72,092 (3.5%) CBC patients, 147 (5.8%) of CBC cases with 1st degree relative | Modest elevation in CBC risk for women with an affected 1st degree relative RR of 1.53                                                                                                                                   |
| Boughey [55] | 2010 | Retrospective cohort     | Median 17.3 years | 385 patients with a positive FH, 385 matched controls                      | Patients with stage I or II BC and a positive family history who underwent CPM had: A 95% reduction in CBC rates; adjusted HR 0.05 (95% CI 0.01–0.19, $p < 0.0001$)                                              |

CPM: contralateral prophylactic mastectomy; BC: breast cancer; BBC: bilateral breast cancer; CBC: contralateral breast cancer; UBC: unilateral breast cancer; AR: absolute risk; SIR: Standardized incidence ratio; FH: family history; RD: risk difference; HR: hazard ratio.
In a retrospective study of 6230 women from high risk families, with or without a known \textit{BRCA1/2} mutation, Rhiem observed a cumulative contralateral breast cancer risk, 25 years after a first breast cancer diagnosis of 44.1% (95% CI 37.6–50.6) in \textit{BRCA1} positive families, 33.5% (95% CI 22.4–44.7) in \textit{BRCA2} positive families and 17.2% (95% CI 14.5–19.9) in \textit{BRCA1/2} negative families [56]. This effect was previously demonstrated in smaller cohort studies linking a higher contralateral breast cancer risk with a family history with and without a young age of first breast cancer diagnosis [51,53].

The age at which the affected relative is diagnosed with their first breast cancer and the presence of bilateral disease impacts on contralateral breast cancer risk. Rhiem further observes that patients diagnosed with breast cancer at age <40 years had a cumulative risk 25 years from primary diagnosis of 55.1% and 38.4% for \textit{BRCA1} and \textit{BRCA2}-positive family history, respectively. The corresponding risk was 28.4% in patients from non-\textit{BRCA} families [56].

The highest risk lies with women who have relatives with early-onset, bilateral breast cancer [52–54,57]. The 10-year absolute risk in individuals whose 1st degree relative received a unilateral breast cancer diagnosis at a young age (<40 years) is similar to that of an individual with a 1st degree relative diagnosed with bilateral breast cancer (13.5% and 14.1% respectively). When there was a combination of a family history of a 1st degree relative, an affected relative with bilateral breast cancer or at a young age (<40 years), the 10-year contralateral breast cancer risk increased significantly to 36% [46]. A similar cumulative risk of contralateral breast cancer by the age of 80 (32%, 95% CI 13–66) was observed in a study of 78,775 breast cancer patients, with a maternal history of bilateral breast cancer [53].

5.2. Contralateral Prophylactic Mastectomy and Risk of Contralateral Breast Cancer

Contralateral prophylactic mastectomy may reduce the risk of contralateral breast cancer in women with an elevated genetic or familial risk [21]. This meta-analysis demonstrated a risk reduction in women with \textit{BRCA}-positive families (HR 0.03; \(p = 0.0005\)). However, only 4% (19/430) of the cohort were non-carriers, with the remaining 96% representing mutation carriers. Fayanju reported a significant reduction in pooled relative (RR 0.04, 95% CI 0.02–0.09) and absolute risk (−24%, 95% CI (−35)–(−12.4)) of metachronous contralateral breast cancer amongst recipients of contralateral prophylactic mastectomy [58]. This analysis included studies with a significant proportion of \textit{BRCA} carriers which may lead to an overestimation of risk. A case-control study of women with stage I/II breast cancer and a positive family history reported a 95% decreased risk (HR 0.05, 95% CI 0.01–0.19; \(p < 0.0001\)) of contralateral breast cancer following contralateral prophylactic mastectomy, at a median follow-up of 17.3 years, compared to a matched cohort of women who did not receive mastectomy. However, this cohort, with either an affected 1st or 2nd degree relative was not screened for mutation status [55].

McDonnell also demonstrated a contralateral breast cancer risk reduction following contralateral prophylactic mastectomy in pre- and postmenopausal women with a strong family history of breast/ovarian cancer i.e., 94.4% (95% CI 87.7–97.9) and 96% (95% CI 85.6–99.5) respectively, at a median follow up of 10 years using the Anderson model [59] to predict the risk [60]. Although the cohort had a strong family history, the patients had not been screened for mutations. Similar to studies with undefined gene carriers within the study population, this data should be interpreted with caution as the effect from contralateral prophylactic mastectomy may be overestimated from competing risks conferred by mutation carriers.

5.3. Contralateral Prophylactic Mastectomy and Survival

The evidence on the effect of contralateral prophylactic mastectomy on disease-free and overall survival is conflicting (Table 4).

A Cochrane review of 1708 women with variable familial risk, who underwent contralateral prophylactic mastectomy, concluded that although this decreased the incidence of contralateral breast cancer, there was no association with survival improvement [61]. The meta-analysis conducted
by Fayanju demonstrated no association with breast-cancer-specific and overall survival, despite a reduction in the risk of distant metastases or recurrence [58]. The lack of survival benefit from contralateral prophylactic mastectomy in breast cancer patients with elevated familial risk is also reported in smaller, retrospective cohort studies [27,62,63] but with notable exceptions. Boughey reported improved overall (HR 0.77, 95% CI 0.60–0.98; p = 0.03) and disease-free survival (HR 0.67, 95% CI 0.54–0.84) on multivariate analysis [55]. In a review of 908 patients receiving against 46,368 not receiving contralateral prophylactic mastectomy, Herrinton demonstrated that mastectomy reduced breast cancer mortality (HR 0.57, 95% CI 0.45–0.72) and overall mortality (HR 0.6, 95% CI 0.5–0.72) across all levels of familial risk [64]. Furthermore, Davies demonstrated that young women (<40 years) with unilateral, stage I disease and a 1st degree relative with bilateral breast cancer, were the only group to have a quality-adjusted life year benefit from contralateral prophylactic mastectomy, which was similar to that of a BRCA1/2 carrier [63].

Table 4. Studies looking at the impact of CPM on CBC and survival in BC patients with elevated familial risk.

| Author       | Year | Study Type          | Follow up | Patients | Findings                                                                 |
|--------------|------|---------------------|-----------|----------|---------------------------------------------------------------------------|
| Akdeniz [33] | 2019 | Meta-analysis       | N/A       | 68 studies | A positive FH of BC was associated with increased CBC risk  
RR = 1.72 (95% CI 1.15–2.57) |
| Engel [16]   | 2019 | Multicentre,        | Median 2.9|          | 10-year cumulative CBC risk for BRCA1/2 non-carriers  
3.6% (95% CI 2.2–5.7)  
Women with ≥2 relatives with BC had an increased risk of CBC, compared to women without any relative affected by BC  
HR 2.35 (95% CI 1.21–4.55)  
ER-negativity was not associated with an increased CBC risk in BRCA1/2 non-carriers |
| Fayanju [58] | 2014 | Meta-analysis       | N/A       | 14/79 studies | Patients with an elevated familial/genetic risk who had CPM (vs no CPM):  
Reduction in pooled RR of mCBC; RR 0.04 (95% CI 0.02–0.09; p < 0.001)  
Reduction in pooled AR of mCBC; RD of −24% (95% CI −35.6 to −12.4; p = 0.013)  
Significant reduction in rates of distant/metastatic recurrence. CPM was not associated with improved OS or BCSS |
| Boughey [55] | 2010 | Retrospective cohort| Median 17.3|          | Patients with stage I/II BC and a positive family history who underwent CPM had:  
A 95% reduction in CBC rates; adjusted HR 0.05 (95% CI 0.01–0.19, p < 0.0001)  
Improved OS (HR 0.77 (95% CI 0.60–0.98, p = 0.03))  
Improved DFS (HR 0.67 (95% CI 0.54–0.84)) |
| McDonnell [60]| 2001| Retrospective cohort| Median 10 |          | CPM conferred a CBC risk-reduction:  
In premenopausal women of 94.4% (95% CI 87.7–97.9)  
In postmenopausal women of 96% (95% CI 85.6–99.5) |
| Herrinton [64]| 2005| Retrospective cohort| Median 5.7|          | Across all levels of familial risk, CPM:  
Reduces breast cancer mortality (HR = 0.57; 95% CI 0.45–0.72)  
Reduces overall mortality (HR = 0.6; 95% CI 0.5–0.72) |
Table 4. Cont.

| Author       | Year | Study Type       | Follow up | Patients                                                                 | Findings                                                                                     |
|--------------|------|------------------|-----------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Peralta [65] | 2001 | Retrospective cohort | Mean 6.8 years | 23/64 (36%) BC patients undergoing CPM and with ≥one affected 1st degree relative (not screened for mutations) | None of the patients undergoing CPM developed a subsequent CBC                                |
| Kiely [62]   | 2010 | Retrospective cohort | Median 8 years | 154/1018 women who underwent CPM, with FH of BC ± BRCA mutations         | Reduced rate of CBC in women who underwent CPM with no apparent benefit in survival          |

CPM: contralateral prophylactic mastectomy; BC: breast cancer; CBC: contralateral breast cancer; mCBC: metachronous contralateral breast cancer; BBC: bilateral breast cancer; UBC: unilateral breast cancer; FH: Family history; RR: relative risk; AR: absolute risk; DFS: disease-free survival; OS: overall survival; BCSS: breast cancer-specific survival; ER: oestrogen receptor; HR: hazard ratio.

6. Young Women with Breast Cancer

6.1. Young Women with Breast Cancer and Contralateral Breast Cancer Risk

The definition of ‘young’ age group in the literature, varies from the “under-35”- to 50 years. Young age at first primary breast cancer diagnosis is associated with an increased contralateral breast cancer risk, poor prognosis and serves as an independent predictor of recurrence and breast-cancer-related death [66–71] (Table 5). Older studies did not account for BRCA mutation carriers, which may confound contralateral breast cancer risk and survival. Furthermore, they do not consider risk-reducing adjuvant therapies. In a retrospective study of 652 patients ≤35 years compared to 2608 women ≥35 years, the relative risk of contralateral breast cancer was 2.48 in the younger, compared to the older group [70]. This finding is supported by Li, who demonstrated an increased HR of 2.8 (95% CI 1.1–6.9), 2.1 (95% CI 1.1–4.4) and 1.9 (95% CI 1.1–3.5) in the ≤29 years, 30–34 years and 35–39 years age groups, compared to women diagnosed at age ≥40 [67]. The contralateral breast cancer risk is further elevated in HER2-overexpressing and triple negative subtypes [70].

Table 5. Studies looking at the impact of CPM on CBC and survival in young women with breast cancer.

| Author       | Year | Study Type       | Median Follow up | Patient Demographics (Age, CPM Status)                                    | Findings                                                                                     |
|--------------|------|------------------|------------------|---------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Chen [2]     | 2019 | Retrospective cohort | 113 months      | <35 years and CPM 811/3083 (26.3%), 35–39 years and CPM 1243/5961 (20.9%) | No difference in BCSS from CPM HR 1.209 (95% CI 0.908–1.610, p = 0.194)                      |
| Yu [72]      | 2018 | Retrospective cohort | 6.9 years       | 910/1806 young patients (18–50 years) with CPM                            | No difference in OS in women with a young age (18–50 years) who had CPM HR 0.93 (95% CI 0.70–1.24; p = 0.627) |
| Pesce [73]   | 2014 | Retrospective cohort | 6.1 years       | 4338/10,289 (29.7%) young women (<45 years) with Stage I/II cancer with CPM | CPM provides no survival benefit in young women (<45 years) Compared to unilateral mastectomy HR 0.93; p = 0.39 With early-stage (T1N0) breast cancer HR 0.85; p = 0.37 With ER-negative breast cancer HR 1.12; p = 0.22 |
| Bedrosian [74] | 2010 | Population based cohort study | 47 months | 3731/27,336 (13.6%) young women (18–49 years) with CPM | CPM offers benefit in BCSS for young women (18–49 years) with early stage, ER-negative breast cancer HR 0.68 (95% CI 0.53–0.69), p < 0.001 |
Table 5. Cont.

| Author               | Year | Study Type         | Median Follow up | Patient Demographics (Age, CPM Status) | Findings                                                                 |
|----------------------|------|--------------------|------------------|----------------------------------------|--------------------------------------------------------------------------|
| Bouchard-Fortier     | 2018 | Population-based cohort | 11 years        | 81/614 (13.2%) young women (<35 years) with CPM | Risk of recurrence (breast/distant) was lower in the CPM group HR 0.61, p = 0.02 |
|                      |      |                    |                  |                                        | No difference in breast cancer-specific mortality from CPM HR 0.73 (95% CI 0.47–1.21) |
| Zeichner             | 2014 | Retrospective cohort | 68 months       | 42/481 (8.73%) young women (<40 years) with CPM | CPM provides a benefit in 10-year overall survival * HR 2.35 (95% CI 1.02–5.41, p = 0.046) |
|                      |      |                    |                  |                                        | * effect not seen at 5-year overall survival                             |
| Lazow                | 2018 | Population-based cohort | Mean 62 months | 4139/11,859 (34.9%) young women (<40 years) with CPM | CPM improves 10-year overall survival HR 0.75 (95% CI 0.59–0.96) p = 0.023 |
| Park                 | 2017 | Population based, national database study | Not stated | 3648 DCIS patients <40 years (25.8% UM; 15.8% CPM) | No overall survival benefit from CPM compared to UM in the <40 years group |

OS: overall survival; CPM: contralateral prophylactic mastectomy; unilateral mastectomy: BCSS: breast-cancer-specific survival.

6.2. Contralateral Prophylactic Mastectomy and Risk of Contralateral Breast Cancer

The younger age group is generally underrepresented in studies evaluating the role of contralateral prophylactic mastectomy. Using a Surveillance, Epidemiology, End Results database analysis of 107,106 women, of whom 8902 (8.3%) underwent contralateral prophylactic mastectomy, Bedrosian conducted a subgroup analysis of young women (<50 years) and the risk of contralateral breast cancer after contralateral prophylactic mastectomy, in both ER-negative and ER-positive, early-stage breast cancer. In ER-positive disease, the cumulative incidence of contralateral breast cancer during the 6-year study period was 0.13% vs. 0.46% (p = 0.07) in the contralateral prophylactic mastectomy vs. non-mastectomy group, and in ER-negative disease, 0.16% vs. 0.90% (p = 0.05) respectively [74]. These results should be interpreted with caution though as the study population was not screened for genetic carriers and also patients with a strong family history were not excluded.

6.3. Contralateral Prophylactic Mastectomy and Survival

There is conflicting data on the impact of contralateral prophylactic mastectomy on survival in this patient group. In a population-based study of 614 women <35 years, 81 (13.2%) of whom were elected for contralateral prophylactic mastectomy, Bouchard-Fortier demonstrated that recurrences, defined as local, regional or distant, were significantly fewer for patients with contralateral prophylactic mastectomy than without (32.1% vs. 52.9%, p < 0.001; HR 0.61; p = 0.02). However, this did not translate to an improvement in breast cancer-specific survival [75].

In an analysis of the National Cancer Database between 2004 and 2014, Lazow demonstrated that after controlling for patient demographics, tumor grade and use of adjuvant therapies, bilateral mastectomy in women <40 years was associated with increased 10-year overall survival (HR 0.75, 95% CI 0.59–0.96; p = 0.023), compared to the unilateral mastectomy group [76]. This trend was also observed in a preceding National Cancer Database review from 1998–2002, demonstrating a 5-year overall survival benefit of 2% in young patients (adjusted HR 0.88, 95% CI 0.83–0.93; p < 0.001) between these two groups [78]. In a retrospective study of 42/481 (8.73%) young women <40 years, who were elected for contralateral prophylactic mastectomy, Zeicher reported that this was associated with improved 10-year overall survival (HR 2.35, 95% CI 1.02–5.41; p = 0.046), although this effect was not demonstrable for 5-year overall survival [71].

There is a suggestion that contralateral prophylactic mastectomy may confer benefit in young women with early-stage, ER-negative breast cancer. In a population-based study of 107,106 breast cancer patients, 3731 (3.48%) of whom were young (18–49 years), contralateral prophylactic mastectomy
was associated with improved disease-specific mortality (HR 0.68, 95% CI 0.53–0.88; \( p = 0.004 \)). This effect was not reproduced in young women with early-stage, ER-positive breast cancer [74].

Other retrospective cohort or population-based studies refute the survival benefit of contralateral prophylactic mastectomy in young women [72,73,75,77]. In a review of 9044 young women (<40 years) with breast cancer, Chen demonstrated no improvement in overall or breast cancer-specific survival [2]. This was supported in a retrospective study of 10,226 patients with invasive lobular carcinoma, demonstrating no overall survival benefit from contralateral prophylactic mastectomy in the 18–50 years group, at a median follow up of 6.9 years [72]. Moreover, in a review of 14,627 women and at median follow-up of 6.1 years, having matched for tumour size/grade, ER status and nodal status, Pesce demonstrated that contralateral prophylactic mastectomy offered no overall survival benefit, in women aged <45 years, with stage I/II breast cancer (HR 0.93, \( p = 0.39 \)) [73].

Overall, these findings should be interpreted with caution as the quality of the data does not allow for definitive conclusions to be drawn.

7. Discussion

Contralateral prophylactic mastectomy is increasingly being performed despite an ambiguity of evidence to support an oncological benefit. In 2007 and 2009, two studies reported that contralateral prophylactic mastectomy rate had increased 148% and 150% among all patients diagnosed with non-invasive and invasive breast cancer respectively [79,80]. Current trends in the U.S.A show an absolute percentage increase in the range of 25% [81]. This trend is modest in European studies suggesting a difference in practice and healthcare environments [82–84]. Nonetheless, this increased utilization of contralateral prophylactic mastectomy is a cause of concern for clinicians because of the associated surgical risks, complications, and psychological and financial burden in the absence of robust evidence to support significant oncological benefits.

Although intuitively it is expected that contralateral prophylactic mastectomy would decrease the risk of contralateral breast cancer, the available data only support this in patients with BRCA1/2 gene mutations [14,26,27]. In women with strong family history or young age at diagnosis, the effect of contralateral prophylactic mastectomy is less well studied and the existing literature should be interpreted with caution because of the potential biases. At present, there are no models that allow for calculation of contralateral breast cancer risk in a polyfactorial model. Such a model might be useful in stratifying risk and aiding physicians to provide precise and unbiased estimation of risk, in order to offer individualized counselling to patients, inform decision-making and mitigate patient overestimation of cancer risk which may drive unnecessary surgery.

Despite the potential decrease in contralateral breast cancer, the effect of contralateral prophylactic mastectomy on oncological outcomes is debatable as studies suggest that this reduction is not translated into survival benefit. Moreover, the role of contralateral prophylactic mastectomy per se as a contributing factor for improved outcomes in women with unilateral breast cancer is difficult to accurately define, as the majority of the available data is of limited quality. Meta-analyses are only as strong as the independent studies they comprise. The majority of studies are retrospective cohorts and based on population/family studies. Therefore, the results should be interpreted with caution because of potential uncontrolled biases. The way to address these issues is with higher quality data but it is unlikely that the future will harbour randomized clinical trials investigating the impact of contralateral prophylactic mastectomy on contralateral breast cancer risk and survival due to patient preference and ethical considerations. One proposal is to set up robust prospective registries to help enhance our knowledge in the field. The majority of existing studies do not account for the significant role conferred by improved systemic therapies and its effect on contralateral breast cancer risk and improved oncological outcomes, factors that merit future research.

Recently, and in order to aid clinicians approach this controversial topic, both the American Society of Breast Surgeons and Association of Breast Surgery published consensus statements on the utilization of contralateral prophylactic mastectomy. Both were aligned on supporting its use in women with
significant contralateral breast cancer risk i.e., BRCA1/2 mutations, patients with a history of mantle field radiation to the chest before age 30 years [85,86]. However, a multidisciplinary, individualised approach is required to help women in their informed decision-making process.

8. Conclusions

In conclusion, contralateral prophylactic mastectomy may be supported in ‘high-risk’ groups as evidence indicates a possible reduction in contralateral breast cancer risk and also potentially improved oncological outcomes. The evidence to demonstrate that this may confer benefit in the other risk groups or in older patients is less established. It is therefore imperative to follow a multidisciplinary, personalised approach, to educate women on the best available evidence and to support individuals in a shared-decision making process.

Funding: This research received no external funding.

Acknowledgments: The authors acknowledge the David Adams library, The Royal Marsden NHS Foundation Trust and The National Institute for Health Research Biomedical Research Centre (NIHR-BRC) for supporting this study.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Bhat, S.; Orucevic, A.; Woody, C.; Heidel, R.E.; Bell, J.L. Evolving Trends and Influencing Factors in Mastectomy Decisions. *Am. Surg.* 2017, 83, 233–238. [PubMed]
2. Chen, H.; Zhang, P.; Zhang, M.; Wang, M.; Bai, F.; Wu, K. Growing Trends of Contralateral Prophylactic Mastectomy and Reconstruction in Young Breast Cancer. *J. Surg. Res.* 2019, 239, 224–232. [CrossRef] [PubMed]
3. Wong, S.M.; Freedman, R.A.; Sagara, Y.; Aydogan, F.; Barry, W.T.; Golshan, M. Growing Use of Contralateral Prophylactic Mastectomy Despite no Improvement in Long-term Survival for Invasive Breast Cancer. *Ann. Surg.* 2017, 265, 581–589. [CrossRef] [PubMed]
4. Pesce, C.E.; Liederbach, E.; Czechura, T.; Winchester, D.J.; Yao, K. Changing surgical trends in young patients with early stage breast cancer, 2003 to 2010: A report from the National Cancer Data Base. *J. Am. Coll. Surg.* 2014, 219, 19–28. [CrossRef] [PubMed]
5. Arrington, A.K.; Jarosek, S.L.; Virmig, B.A.; Habermann, E.B.; Tuttle, T.M. Patient and surgeon characteristics associated with increased use of contralateral prophylactic mastectomy in patients with breast cancer. *Ann. Surg. Oncol.* 2009, 16, 2697–2704. [CrossRef]
6. Buchanan, P.J.; Abdulghani, M.; Waljee, J.F.; Kozlow, J.H.; Sabel, M.S.; Newman, L.A.; Chung, K.C.; Momoh, A.O. An Analysis of the Decisions Made for Contralateral Prophylactic Mastectomy and Breast Reconstruction. *Plast. Reconstr. Surg.* 2016, 138, 29–40. [CrossRef]
7. Brewster, A.M.; Parker, P.A. Current knowledge on contralateral prophylactic mastectomy among women with sporadic breast cancer. *Oncologist* 2011, 16, 935–941. [CrossRef]
8. Chung, A.; Huynh, K.; Lawrence, C.; Sim, M.S.; Giuliano, A. Comparison of patient characteristics and outcomes of contralateral prophylactic mastectomy and unilateral total mastectomy in breast cancer patients. *Ann. Surg. Oncol.* 2012, 19, 2600–2606. [CrossRef]
9. Ager, B.; Butow, P.; Jansen, J.; Phillips, K.A.; Porter, D. Contralateral prophylactic mastectomy (CPM): A systematic review of patient reported factors and psychological predictors influencing choice and satisfaction. *Breast* 2016, 28, 107–120. [CrossRef]
10. Patient Request for Contralateral Prophylactic Mastectomy Is Due to A False Perception of Increased Risk at the Time of Initial Diagnosis. Available online: https://www.ecco-org.eu/ecco_content/EBCC7_abstractbook/files/assets/seo/page134.html (accessed on 2 February 2019).
11. Butow, P. Applying social-cognition models to understand women’s hypothetical intentions for contralateral prophylactic mastectomy. *Proc. Asia Pac. J. Clin. Oncol.* 2014, 10, 189.
12. Jaggi, R.; Hawley, S.T.; Griffith, K.A.; Janz, N.K.; Kurian, A.W.; Ward, K.C.; Hamilton, A.S.; Morrow, M.; Katz, S.J. Contralateral Prophylactic Mastectomy Decisions in a Population-Based Sample of Patients With Early-Stage Breast Cancer. *JAMA Surg.* 2017, 152, 274–282. [CrossRef] [PubMed]
13. Lizarraga, I.M.; Sugg, S.L.; Weigel, R.J.; Scott-Conner, C.E. Review of risk factors for the development of contralateral breast cancer. *Am. J. Surg.* 2013, 206, 704–708. [CrossRef] [PubMed]

14. Valachis, A.; Nearchou, A.D.; Lind, P. Surgical management of breast cancer in BRCA-mutation carriers: A systematic review and meta-analysis. *Breast Cancer Res. Treat.* 2014, 144, 443–455. [CrossRef] [PubMed]

15. Van den Broek, A.J.; van’t Veer, L.J.; Hooning, M.J.; Cornelissen, S.; Broeks, A.; Rutgers, E.J.; Smit, V.T.; Cornelisse, C.J.; van Beek, M.; Janssen-Heijnen, M.L.; et al. Impact of Age at Primary Breast Cancer on Contralateral Breast Cancer Risk in BRCA1/2 Mutation Carriers. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 2016, 34, 409–418. [CrossRef] [PubMed]

16. Engel, C.; Fischer, C.; Zachariae, S.; Bucksch, K.; Rhiem, K.; Giesecke, J.; Herold, N.; Wappenschmidt, B.; Hubbel, V.; Maringa, M.; et al. Breast cancer risk in BRCA1/2 mutation carriers and noncarriers under prospective intensified surveillance. *Int. J. Cancer* 2019. [CrossRef] [PubMed]

17. Verhoog, L.C.; Brekelmans, C.T.; Seynaeve, C.; Meijers-Heijboer, E.J.; Klijn, J.G. Contralateral breast cancer risk is influenced by the age at onset in BRCA1-associated breast cancer. *Br. J. Cancer* 2000, 83, 384–386. [CrossRef]

18. Malone, K.E.; Daling, J.R.; Doody, D.R.; Hsu, L.; Bernstein, L.; Coates, R.J.; Marchbanks, P.A.; Simon, M.S.; McDonald, J.A.; Norman, S.A.; et al. Prevalence and predictors of BRCA1 and BRCA2 mutations in a population-based study of breast cancer in white and black American women ages 35 to 64 years. *Cancer Res.* 2006, 66, 8297–8308. [CrossRef]

19. Graeser, M.K.; Engel, C.; Rhiem, K.; Gadzicki, D.; Bick, U.; Kast, K.; Froster, U.G.; Schlehe, B.; Bechtold, A.; Arnold, N.; et al. Contralateral breast cancer risk in BRCA1 and BRCA2 mutation carriers. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 2009, 27, 5887–5892. [CrossRef]

20. Kuchenbaecker, K.B.; Hopper, J.L.; Barnes, D.R.; Phillips, K.A.; Mooij, T.M.; Roos-Blom, M.J.; Jervis, S.; van Leeuwen, F.E.; Milne, R.L.; Andrieu, N.; et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. *JAMA* 2017, 317, 2402–2416. [CrossRef]

21. Metcalfe, K.; Lynch, H.T.; Ghadirian, P.; Tung, N.; Olivotto, I.; Warner, E.; Olopade, O.I.; Eisen, A.; Weber, B.; McLennan, J.; et al. Contralateral breast cancer in BRCA1 and BRCA2 mutation carriers. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 2004, 22, 2328–2335. [CrossRef]

22. Pierce, L.J.; Haftfy, B.G. Radiotherapy in the treatment of hereditary breast cancer. *Semin. Radiat. Oncol.* 2011, 21, 43–50. [CrossRef] [PubMed]

23. Robson, M.; Gilewski, T.; Haas, B.; Levin, D.; Borgen, P.; Rajan, P.; Hirschaut, Y.; Pressman, P.; Rosen, P.P.; Lesser, M.L.; et al. BRCA-associated breast cancer in young women. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 1998, 16, 1642–1649. [CrossRef] [PubMed]

24. Mavaddat, N.; Peock, S.; Frost, D.; Ellis, S.; Platte, R.; Fineberg, R.; Evans, D.G.; Izatt, L.; Eeles, R.A.; Adlard, J.; et al. Cancer risks for BRCA1 and BRCA2 mutation carriers: Results from prospective analysis of EMBRACE. *J. Natl. Cancer Inst.* 2013, 105, 812–822. [CrossRef] [PubMed]

25. Robson, M.E.; Chappuis, P.O.; Satagopan, J.; Wong, N.; Boyd, J.; Goffin, J.R.; Hudis, C.; Roberge, D.; Norton, L.; Begin, L.R.; et al. A combined analysis of outcome following breast cancer: Differences in survival based on BRCA1/BRCA2 mutation status and administration of adjuvant treatment. *Breast Cancer Res.* 2004, 6, R8–R17. [CrossRef] [PubMed]

26. Li, X.; You, R.; Wang, X.; Liu, C.; Xu, Z.; Zhou, J.; Yu, B.; Xu, T.; Cai, H.; Zhou, Q. Effectiveness of Prophylactic Surgeries in BRCA1 or BRCA2 Mutation Carriers: A Meta-analysis and Systematic Review. *Clin. Cancer Res.* 2016, 22, 3971–3981. [CrossRef] [PubMed]

27. Van Sprundel, T.C.; Schmidt, M.K.; Rookus, M.A.; Brohet, R.; van Asperen, C.J.; Rutgers, E.J.; Van’t Veer, L.J.; Tollenaar, R.A. Risk reduction of contralateral breast cancer and survival after contralateral prophylactic mastectomy in BRCA1 or BRCA2 mutation carriers. *Br. J. Cancer* 2005, 93, 287–292. [CrossRef] [PubMed]

28. Brekelmans, C.T.; Tilanus-Linthorst, M.M.; Seynaeve, C.; vd Ouweland, A.; Menke-Pluymers, M.B.; Bartels, C.C.; Kriege, M.; van Geel, A.N.; Burger, C.W.; Eggermont, A.M.; et al. Tumour characteristics, survival and prognostic factors of hereditary breast cancer from BRCA2-, BRCA1- and non-BRCA1/2 families as compared to sporadic breast cancer cases. *Eur. J. Cancer* 2007, 43, 867–876. [CrossRef]

29. Metcalfe, K.; Gershman, S.; Ghadirian, P.; Lynch, H.T.; Snyder, C.; Tung, N.; Kim-Sing, C.; Eisen, A.; Foulkes, W.D.; Rosen, B.; et al. Contralateral mastectomy and survival after breast cancer in carriers of BRCA1 and BRCA2 mutations: Retrospective analysis. *BMJ (Clin. Res. Ed.)* 2014, 348, g226. [CrossRef]
30. Heemskerk-Gerritsen, B.A.; Rookus, M.A.; Aalfs, C.M.; Ausems, M.G.; Collee, J.M.; Jansen, L.; Kets, C.M.; Keymeulen, K.B.; Koppert, L.B.; Meijers-Heijboer, H.E.; et al. Improved overall survival after contralateral risk-reducing mastectomy in BRCA1/2 mutation carriers with a history of unilateral breast cancer: A prospective analysis. *Int. J. Cancer* 2015, 136, 668–677. [CrossRef]

31. Evans, D.G.; Ingham, S.L.; Baildam, A.; Ross, G.L.; Laloo, F.; Buchan, I.; Howell, A. Contralateral mastectomy improves survival in women with BRCA1/2-associated breast cancer. *Br. J. Cancer* 2013, 140, 135–142. [CrossRef]

32. Copson, E.R.; Maishman, T.C.; Tapper, W.J.; Cutress, R.I.; Greville-Heygate, S.; Altman, D.G.; Eccles, B.; Gerty, S.; Durcan, L.T.; Jones, L.; et al. Germline BRCA mutation status and outcome in young-onset breast cancer (POSH): A prospective cohort study. *Lancet Oncol. 2018*, 19, 169–180. [CrossRef]

33. Akdeniz, D.; Schmidt, M.K.; Seynaeve, C.M.; McCool, D.; Giardiello, D.; van den Broek, A.J.; Hauptmann, M.; Steyerberg, E.W.; Hooning, M.J. Risk factors for metachronous contralateral breast cancer: A systematic review and meta-analysis. *Br. J. Cancer* 2019, 44, 1–14. [CrossRef] [PubMed]

34. Fletcher, O.; Johnson, N.; Dos Santos Silva, I.; Kilpivaara, O.; Aittomäki, K.; Blomqvist, C.; Nevanlinna, H.; Wäsielowski, M.; Meijers-Heijboer, H.; Broeks, A.; et al. Family history, genetic testing, and clinical risk prediction: Pooled analysis of CHEK2*1100delC in 1828 bilateral breast cancers and 7030 controls. *Cancer Epidemiol. Biomark.* 2009, 18, 230–234. [CrossRef] [PubMed]

35. Schmidt, M.K.; Hogervorst, F.; van Hien, R.; Cornelissen, S.; Broeks, A.; Adank, M.A.; Meijers, H.; Waisfiz, Q.; Hollestelle, A.; Schutte, M.; et al. Age- and Tumor Subtype-Specific Breast Cancer Risk Estimates for CHEK2*1100delC Carriers. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 2016, 34, 2750–2760. [CrossRef] [PubMed]

36. Schmidt, M.K.; Tollenaar, R.A.; de Kemp, S.R.; Broeks, A.; Cornelisse, C.J.; Smit, V.T.; Peterse, J.L.; van Leeuwen, F.E.; Van’t Veer, L.J. Breast cancer survival and tumor characteristics in premenopausal women carrying the CHEK2*1100delC germline mutation. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 2007, 25, 64–69. [CrossRef] [PubMed]

37. Weis cher, M.; Nordestgaard, B.G.; Pharoah, P.; Bolla, M.K.; Nevanlinna, H.; Van’t Veer, L.J.; Garcia-Closas, M.; Hopper, J.L.; Hall, P.; Andrulis, I.L.; et al. CHEK2*1100delC heterozygosity in women with breast cancer associated with early death, breast cancer-specific death, and increased risk of a second breast cancer. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* 2012, 30, 4308–4316. [CrossRef] [PubMed]

38. Meyer, A.; Dork, T.; Sohn, C.; Karstens, J.H.; Bremer, M. Breast cancer in patients carrying a germ-line CHEK2 mutation: Outcome after breast conserving surgery and adjuvant radiotherapy. *Radiother. Oncol. J. Eur. Soc.* 2007, 82, 349–353. [CrossRef]

39. Krieger, M.; Hollestelle, A.; Jager, A.; Huijts, P.E.; Berns, E.M.; Smeu werts, A.M.; Meijer-van Gelder, M.E.; Collee, J.M.; Devilee, P.; Hooning, M.J.; et al. Survival and contralateral breast cancer in CHEK2*1100delC breast cancer patients: Impact of adjuvant chemotherapy. *Br. J. Cancer 2014*, 111, 1004–1013. [CrossRef]

40. Mellemkjaer, L.; Dahl, C.; Olsen, J.H.; Bertelsen, L.; Guldberg, P.; Christensen, J.; Berre sen-Dale, A.L.; Stovall, M.; Langholz, B.; Bernstein, L.; et al. Risk for contralateral breast cancer among carriers of the CHEK2*1100delC mutation in the WECARE Study. *Br. J. Cancer 2008*, 98, 728–733. [CrossRef]

41. Broeks, A.; de Witte, L.; Nooijen, A.; Huseinovic, A.; Klijn, J.G.; van Leeuwen, F.E.; Russell, N.S.; van’t Veer, L.J. Excess risk for contralateral breast cancer in CHEK2*1100delC germline mutation carriers. *Br. J. Cancer Res. Treat.* 2004, 83, 93–94. [CrossRef]

42. Concannon, P.; Haile, R.W.; Borresen-Dale, A.L.; Rosenste in, B.S.; Gatti, R.A.; Teraoka, S.N.; Diep, T.A.; Jansen, L.; Atencio, D.P.; Langholz, B.; et al. Variants in the ATM gene associated with a reduced risk of contralateral breast cancer. *Cancer Res. 2008*, 68, 6486–6491. [CrossRef]

43. Bernstein, J.L.; Concannon, P. ATM, radiation, and the risk of second primary breast cancer. *Int. J. Radiat. Biol.* 2017, 93, 1121–1127. [CrossRef] [PubMed]

44. Broeks, A.; Braaf, L.M.; Huseinovic, A.; Schmidt, M.K.; Russell, N.S.; van Leeuwen, F.E.; Hogervorst, F.B.; van’t Veer, L.J. The spectrum of ATM missense variants and their contribution to contralateral breast cancer. *Br. J. Cancer Res. Treat.* 2008, 107, 243–248. [CrossRef] [PubMed]

45. De Bock, G.H.; Schutte, M.; Krol-Warmerdam, E.M.; Seynaeve, C.; Blom, J.; Brekelmans, C.T.; Meijers-Heijboer, H.; Van Asperen, C.J.; Cornelisse, C.J.; Devilee, P.; et al. Tumour characteristics and prognosis of breast cancer patients carrying the germline CHEK2*1100delC variant. *J. Med. Genet.* 2004, 41, 731–735. [CrossRef] [PubMed]
46. Reiner, A.S.; Sisti, J.; John, E.M.; Lynch, C.F.; Brooks, J.D.; Mellemkjaer, L.; Boice, J.D.; Knight, J.A.; Concannon, P.; Capanu, M.; et al. Breast Cancer Family History and Contralateral Breast Cancer Risk in Young Women: An Update From the Women’s Environmental Cancer and Radiation Epidemiology Study. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2018, 36, 1513–1520. [CrossRef] [PubMed]

47. Begg, C.B.; Haile, R.W.; Borg, A.; Malone, K.E.; Concannon, P.; Thomas, D.C.; Langholz, B.; Bernstein, L.; Olsen, J.H.; Lynch, C.F.; et al. Variation of breast cancer risk among BRCA1/2 carriers. JAMA 2008, 299, 194–201. [CrossRef] [PubMed]

48. Reiner, A.S.; John, E.M.; Brooks, J.D.; Lynch, C.F.; Bernstein, L.; Mellemkjaer, L.; Malone, K.E.; Knight, J.A.; Capanu, M.; Teraoka, S.N.; et al. Risk of asynchronous contralateral breast cancer in noncarriers of BRCA1 and BRCA2 mutations with a family history of breast cancer: A report from the Women’s Environmental Cancer and Radiation Epidemiology Study. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2013, 31, 433–439. [CrossRef] [PubMed]

49. Bernstein, J.L.; Thomas, D.C.; Shore, R.E.; Robson, M.; Boice, J.D.; Stovall, M.; Andersson, M.; Bernstein, L.; Malone, K.E.; Reiner, A.S.; et al. Contralateral breast cancer after radiotherapy among BRCA1 and BRCA2 mutation carriers: A WECARE study report. Eur. J. Cancer 2013, 49, 2979–2985. [CrossRef]

50. Pharoah, P. Family history and the risk of breast cancer: A systematic review and meta-analysis. Int. J. Cancer 1997, 71, 800–809. [CrossRef]

51. Bernstein, J.L.; Thompson, W.D.; Risch, N.; Holford, T.R. Risk factors predicting the incidence of second primary breast cancer among women diagnosed with a first primary breast cancer. Am. J. Epidemiol. 1992, 136, 925–936. [CrossRef]

52. Ji, J.; Hemminki, K. Risk for contralateral breast cancers in a population covered by mammography: Effects of family history, age at diagnosis and histology. Breast Cancer Res. Treat. 2007, 105, 229–236. [CrossRef]

53. Narod, S.A.; Kharazmi, E.; Fallah, M.; Sundquist, K.; Hemminki, K. The risk of contralateral breast cancer in daughters of women with and without breast cancer. Clin. Genet. 2016, 89, 332–335. [CrossRef] [PubMed]

54. Vaittinen, P.; Hemminki, K. Risk factors and age-incidence relationships for contralateral breast cancer. Int. J. Cancer 2000, 88, 998–1002. [CrossRef]

55. Boughey, J.C.; Hoskin, T.L.; Degnim, A.C.; Sellers, T.A.; Johnson, J.L.; Kasner, M.J.; Hartmann, L.C.; Frost, M.H. Contralateral prophylactic mastectomy is associated with a survival advantage in high-risk women with a personal history of breast cancer. Ann. Surg. Oncol. 2010, 17, 2702–2709. [CrossRef] [PubMed]

56. Rhiem, K.; Engel, C.; Graeser, M.; Zachariae, S.; Kast, K.; Kiechle, M.; Ditsch, N.; Janni, W.; Mundhenke, C.; Golatta, M.; et al. The risk of contralateral breast cancer in patients from BRCA1/2 negative high risk families as compared to patients from BRCA1 or BRCA2 positive families: A retrospective cohort study. Breast Cancer Res. 2012, 14, R156. [CrossRef] [PubMed]

57. Bernstein, J.L.; Thompson, W.D.; Risch, N.; Holford, T.R. The genetic epidemiology of second primary breast cancer. Am. J. Epidemiol. 1992, 136, 937–948. [CrossRef]

58. Fayanju, O.M.; Stoll, C.R.; Fowler, S.; Colditz, G.A.; Margenthaler, J.A. Contralateral prophylactic mastectomy after unilateral breast cancer: A systematic review and meta-analysis. Ann. Surg. 2014, 260, 1000–1010. [CrossRef]

59. Anderson, D.E.; Badzioch, M.D. Risk of familial breast cancer. Cancer 1985, 56, 383–387. [CrossRef]

60. McDonnell, S.K.; Schaid, D.J.; Myers, J.L.; Grant, C.S.; Donohue, J.H.; Woods, J.E.; Frost, M.H.; Johnson, J.L.; Sitta, D.L.; Sleczak, J.M.; et al. Efficacy of contralateral prophylactic mastectomy in women with a personal and family history of breast cancer. J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol. 2001, 19, 3938–3943. [CrossRef]

61. Lostumbo, L.; Carbine, N.E.; Wallace, J. Prophylactic mastectomy for the prevention of breast cancer. Cochrane Database Syst. Rev. 2010, CD002748. [CrossRef]

62. Kiely, B.E.; Jenkins, M.A.; McKinley, J.M.; Friedlander, M.L.; Weideman, P.; Milne, R.L.; McLachlan, S.A.; Hopper, J.L.; Phillips, K.A. Contralateral risk-reducing mastectomy in BRCA1 and BRCA2 mutation carriers and other high-risk women in the Kathleen Cunningham Foundation Consortium for Research into Familial Breast Cancer (kConFab). Breast Cancer Res. Treat. 2010, 120, 715–723. [CrossRef]

63. Davies, K.R.; Brewster, A.M.; Bedrosian, I.; Parker, P.A.; Crosby, M.A.; Peterson, S.K.; Shen, Y.; Volk, R.J.; Cantor, S.B. Outcomes of contralateral prophylactic mastectomy in relation to familial history: A decision analysis (BRCR-D-16-00033). Breast Cancer Res. 2016, 18, 93. [CrossRef] [PubMed]
64. Herrinton, L.J.; Barlow, W.E.; Yu, O.; Geiger, A.M.; Elmore, J.G.; Barton, M.B.; Harris, E.L.; Rolnick, S.; Pardee, R.; Hussn, G.; et al. Efficacy of prophylactic mastectomy in women with unilateral breast cancer: A cancer research network project. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2005**, *23*, 4275–4286. [CrossRef] [PubMed]

65. Peralta, E.A.; Ellenhorn, J.D.; Wagman, L.D.; Dagis, A.; Andersen, J.S.; Chu, D.Z. Contralateral prophylactic mastectomy improves the outcome of selected patients undergoing mastectomy for breast cancer. *Am. J. Surg.* **2000**, *180*, 439–445. [CrossRef]

66. Kurian, A.W.; McClure, L.A.; John, E.M.; Horn-Ross, P.L.; Ford, J.M.; Clarke, C.A. Second primary breast cancer occurrence according to hormonal receptor status. *J. Natl. Cancer Inst.* **2009**, *101*, 1058–1065. [CrossRef]

67. Li, C.I.; Malone, K.E.; Porter, P.L.; Daling, J.R. Epidemiologic and molecular risk factors for contralateral breast cancer among younger women. *Br. J. Cancer* **2003**, *89*, 513–518. [CrossRef]

68. Healey, E.A.; Cook, E.F.; Oray, E.J.; Schnitt, S.J.; Connolly, J.L.; Harris, J.R. Contralateral breast cancer: Clinical characteristics and impact on prognosis. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **1993**, *11*, 1545–1552. [CrossRef]

69. Vichapat, V.; Gillett, C.; Fentiman, I.S.; Tutt, A.; Holmberg, L.; Luchtenborg, M. Risk factors for metachronous contralateral breast cancer suggest two aetiologic pathways. *Eur. J. Cancer* **2011**, *47*, 1919–1927. [CrossRef]

70. Yoon, T.I.; Kwak, B.S.; Yi, O.V.; Kim, S.; Um, E.; Yun, K.W.; Shin, H.N.; Lee, S.; Sohn, G.; Chung, I.Y.; et al. Age-related risk factors associated with primary contralateral breast cancer among younger women versus older women. *Breast Cancer Res. Treat.* **2019**, *173*, 657–665. [CrossRef]

71. Zeichner, S.B.; Zeichner, S.B.; Ruiz, A.L.; Markward, N.J.; Rodriguez, E. Improved long-term survival with contralateral prophylactic mastectomy among women. *Asia Pac. J. Cancer Prev.* **2014**, *15*, 1155–1162. [CrossRef]

72. Yu, T.J.; Liu, Y.Y.; Hu, X.; Di, G.H. No survival improvement of contralateral prophylactic mastectomy among women with invasive lobular carcinoma. *J. Surg. Oncol.* **2018**, *118*, 928–935. [CrossRef] [PubMed]

73. Pesce, C.; Liederbach, E.; Wang, C.; Lapin, B.; Winchester, D.J.; Yao, K. Contralateral prophylactic mastectomy provides no survival benefit in young women with estrogen receptor-negative breast cancer. *Ann. Surg. Oncol.* **2014**, *21*, 3231–3239. [CrossRef]

74. Bedrosian, I.; Hu, C.Y.; Chang, G.J. Population-based study of contralateral prophylactic mastectomy and survival outcomes of breast cancer patients. *J. Natl. Cancer Inst.* **2010**, *102*, 401–409. [CrossRef] [PubMed]

75. Bouchard-Fortier, A.; Baxter, N.N.; Sutradhar, R.; Fernandez, K.; Camacho, X.; Graham, P.; Quan, M.L. Contralateral prophylactic mastectomy in young women with breast cancer: A population-based analysis of predictive factors and clinical impact. *Curr. Oncol.* **2018**, *25*, e562–e568. [CrossRef] [PubMed]

76. Lazow, S.P.; Riba, L.; Alapati, A.; James, T.A. Comparison of breast-conserving therapy vs mastectomy in women under age 40: National trends and potential survival implications. *Breast J.* **2019**, *25*, 578–584. [CrossRef]

77. Park, H.L.; Chang, J.; Lal, G.; Lal, K.; Ziogas, A.; Anton-Culver, H. Trends in Treatment Patterns and Clinical Outcomes in Young Women Diagnosed With Ductal Carcinoma In Situ. *Clin. Breast Cancer* **2018**, *18*, e179–e185. [CrossRef]

78. Yao, K.; Winchester, D.J.; Czechura, T.; Hsu, D. Contralateral prophylactic mastectomy and survival: Report from the National Cancer Data Base, 1998–2002. *Breast Cancer Res. Treat.* **2013**, *142*, 465–476. [CrossRef]

79. Tuttle, T.M.; Habermann, E.B.; Grund, E.H.; Morris, T.J.; Virmig, B.A. Increasing use of contralateral prophylactic mastectomy for breast cancer patients: A trend toward more aggressive surgical treatment. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2007**, *25*, 5203–5209. [CrossRef]

80. Tuttle, T.M.; Jarosek, S.; Habermann, E.B.; Arrington, A.; Abraham, A.; Morris, T.J.; Virmig, B.A. Increasing rates of contralateral prophylactic mastectomy among patients with ductal carcinoma in situ. *J. Clin. Oncol. Off. J. Am. Soc. Clin. Oncol.* **2009**, *27*, 1362–1367. [CrossRef]

81. Kummerow, K.L.; Du, L.; Penske, D.F.; Shtyr, Y.; Hooks, M.A. Nationwide trends in mastectomy for early-stage breast cancer. *JAMA Surg.* **2015**, *150*, 9–16. [CrossRef]

82. Guth, U.; Myrick, M.E.; Viehl, C.T.; Weber, W.P.; Lardi, A.M.; Schmid, S.M. Increasing rates of contralateral prophylactic mastectomy—A trend made in USA? *Eur. J. Surg. Oncol.* *J. Eur. Soc. Surg. Oncol. Br. Assoc. Surg. Oncol.* **2012**, *38*, 296–301. [CrossRef] [PubMed]
83. Fancellu, A.; Sanna, V.; Cottu, P.; Feo, C.F.; Scanu, A.M.; Farina, G.; Bulla, A.; Spanu, A.; Paliogiannis, P.; Porcu, A. Mastectomy patterns, but not rates, are changing in the treatment of early breast cancer. Experience of a single European institution on 2315 consecutive patients. *Breast* 2018, 39, 1–7. [CrossRef] [PubMed]

84. Neuburger, J.; Macneill, F.; Jeevan, R.; van der Meulen, J.H.; Cromwell, D.A. Trends in the use of bilateral mastectomy in England from 2002 to 2011: Retrospective analysis of hospital episode statistics. *BMJ Open* 2013, 3. [CrossRef] [PubMed]

85. Boughey, J.C.; Attai, D.J.; Chen, S.L.; Cody, H.S.; Dietz, J.R.; Feldman, S.M.; Greenberg, C.C.; Kass, R.B.; Landercasper, J.; Lemaine, V.; et al. Contralateral Prophylactic Mastectomy Consensus Statement from the American Society of Breast Surgeons: Additional Considerations and a Framework for Shared Decision Making. *Ann. Surg. Oncol.* 2016, 23, 3106–3111. [CrossRef]

86. ABS Summary Statement Contralateral Mastectomy for Unilateral Breast Cancer. Available online: [https://associationofbreastsurgery.org.uk/media/63462/contralateral-mastectomy-abs-summary-documen.pdf](https://associationofbreastsurgery.org.uk/media/63462/contralateral-mastectomy-abs-summary-documen.pdf) (accessed on 15 February 2019).

© 2020 by the authors. Licensee MDPI, Basel, Switzerland. This article is an open access article distributed under the terms and conditions of the Creative Commons Attribution (CC BY) license (http://creativecommons.org/licenses/by/4.0/).