The melanoma – breast cancer association: an overview of their ‘Second Primary Cancers’ and the epidemiological, genetic and biological correlations

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Table of Contents

1.0 Introduction	4
2.0 Methods	6
3.0 Results and Discussion	7
3.1 Second Primary Cancers Following Breast Cancer	7
3.2 Melanoma Following Breast Cancer	7
3.3 Second Primary Cancers Following Melanoma	10
3.4 Breast cancer following melanoma	10
3.5 Associated Factors	12
3.5.1 Genetics	12
3.5.2 Biological Factors – Oestrogen Receptors	15
3.5.3 Surveillance Bias	16
4.0 Conclusion	17

Highlights:

- 1- There is a significant risk association between breast cancers and melanomas.
- 2- Younger age and use of radiation are potential risk factors for second primary cancers.
- 3- The positive breast cancer-melanoma association can be genetically dependent.
- 4- Socio-cultural factors and surveillance bias may be attributed to previous findings.

Graphic Abstract

ABSTRACT

This study reviews the relevant epidemiological studies associating cutaneous melanoma and breast carcinomas and provides an overview of the possible genetic, biological and bias factors that underpin this relationship. Standardised incidence ratio (SIR) for primary cutaneous melanoma after breast carcinoma ranged from 1.16 to 5.13 and ranged from 1.03 to 4.10 for primary breast carcinoma after cutaneous melanoma. Epidemiological studies highlight age, gender and use of radiotherapy and chemotherapy as potential risk factors for second primary cancers (SPCs). Mutations in BRCA2, CDKN2A, CDK4 and BAP1 may partly underlie any SPC association. The impact of socio-cultural factors and surveillance bias may be attributed to the findings of SPC partially or entirely. In conclusion, this study has highlighted the association between breast carcinoma and melanoma and identified various factors for further research and the optimised management of patients with both cancers.

Keywords: cutaneous melanoma; breast cancer; second primary cancers; epidemiology; genetics

1.0 INTRODUCTION

The enhanced focus of research and public health policy on the diagnosis and management of patients with cancer have notably improved cancer survival worldwide (1). In recent years, there has been a shift in focus towards the effective follow-up of cancer survivors. This is due to epidemiological studies that have observed an elevated risk of developing second primary cancers (SPCs) in patients who have received a previous cancer diagnosis in their lifetime (2). SPC is a term applied to a new primary cancer that arises independently from a treated or untreated pre-existing cancer and not as a result of resurgence or metastasis (2). SPCs are thought to occur due to treatment-related, lifestyle, environmental or genetic factors (3). Compared to other cancers, both melanoma and breast cancers are known to have significant relationships with SPCs and to occur as SPCs themselves (4).

Cutaneous melanomas are potentially fatal malignant neoplasms that differentiate from melanocytes. The highest health burden from melanoma is in Australasian, North American and European populations which are related to recreational sun exposure and propensity to sunburn (5). Early detection and preventive measures have reduced the incidence of advanced melanoma while increasing the diagnosis of early-stage diseases (6). While incidence rates continue to climb for breast carcinomas worldwide, there is considerable progress in improving outcomes in high-income countries through the implementation of effective screening protocols (7). Patients who are detected with early-stage melanoma and breast carcinomas carry 5-year survival rates of 99% and 90% respectively. Improvements to survival rates for both cancers are attributed to early detection combined with effective treatment (7). Management focus has shifted towards the long-term morbidity and mortality outcomes of these patients.

In recent years, many registry and hospital-based studies have highlighted the increased risk of second primary cancers for the increased number of survivors of breast carcinoma and melanoma (8-14). Many of these studies have also noted a mutual association between melanomas and breast carcinomas despite differences in predisposing factors (Table 1) (10, 14).

This association was first highlighted in 1975 by Lokich, who noted five patients with both breast carcinoma and melanoma. Of these five patients, four had breast cancer before melanoma (15). Subsequent studies have attempted to elucidate the epidemiological nature of this association, as well as potential genetic, biological and treatment-related factors (16, 17). Some studies have speculated that the correlation found between the two cancers may be attributed to surveillance bias (8, 10, 18). Quantifying the association between melanoma and breast cancers is vital for appropriate clinical management of survivors and for identifying potential risk factors. This study aims to review the association between melanoma and breast carcinoma and provide an overview of the possible genetic, biological and bias factors that may underpin these findings.

2.0 METHODS

Relevant research concerning second primary cutaneous melanoma after breast cancer or second primary breast cancer after cutaneous melanoma were identified using PubMed, Embase and Web of Science databases. Articles were eligible for consideration in this literature review if they were full text, written from 1975 (when a possible link between breast carcinoma and melanoma was first suggested) to the present and in English. Articles excluded were those written earlier than 1975, were not full text or not in English. Only cutaneous melanomas were included in the review. Search terms were kept broad to ensure all relevant studies were identified. Literature search used terms such as “breast carcinoma”, “second or secondary” and “melanoma”. Out of 465 articles reviewed, 119 were relevant to cutaneous melanoma or breast cancer diagnoses after an initial cutaneous melanoma or breast cancer. Data were extracted from 29 papers that reported a standardised incidence ratio and summarised into tables. Review Manager 5.3 was utilised to construct box and whisker plots. Boxes represent the standardised incidence ratio reported, and whiskers reflect the provided confidence interval. Where overlap existed between the melanoma cases reported in studies, the paper with the highest number of melanoma cases was used.

3.0 RESULTS AND DISCUSSION

3.1 Second Primary Cancers Following Breast Cancer

There is strong evidence in the literature for the association between breast cancer and the development of SPCs (19-22). A meta-analysis in 2015 of thirteen studies combining 1,346,671 primary female breast cancer survivors found a 17% increase in the risk of developing a new primary non-breast cancer in comparison to those that had never received a breast carcinoma diagnosis (22). Sites of second primary cancers consistently reported include the soft tissue (sarcoma) (SIR range 2.25-13) (11, 23-25), ovary (SIR range 1.6-5.7) (11, 12, 18, 21, 23-31), thyroid gland (SIR range 1.54-1.62) (12, 21, 24, 32), endometrium (SIR range 1.3-1.52) (11, 12, 21, 23, 24, 27, 29, 30, 32, 33), leukaemia (SIR range 1.2-3.1) (11, 12, 23, 29) and lung (SIR range 1.2-1.24) (18, 19, 21, 25, 29, 32, 34). Studies have postulated the likely causes for these associations. These include breast cancer tamoxifen-treatment and the occurrence of endometrial cancer (35), breast cancer radiation-treatment and occurrence of thyroid cancer (36), lung and soft tissue cancers that arise from radiation-therapy to the chest wall or breast bed (37), cytotoxic chemotherapy and acute myeloid leukaemia (38) and a genetic predisposition for ovarian cancer amongst breast cancer patients (39).

3.2 Melanoma Following Breast Cancer

The occurrence of melanoma in women with a history of breast cancer is becoming evident in the literature (Table 2). While many registry-based and hospital-based studies have concluded standardised incidence ratios (SIRs) ranging from 1.16 to 5.13, some have found little or no significant increase in risk (Figure 1).

Mellemkjaer et al. utilised 13 population-based cancer registries in Europe, Canada, Australia and Singapore to conduct the most extensive study to date, investigating the risk of second primary cancers in breast cancer survivors (40). Among the 525,527 women, 1,135

developed a second primary melanoma equating to a SIR of 1.29 (40). A positive association was found to be consistent among different cancer registries (40). Like other investigations, the risk of melanoma remained constant throughout follow-up (11, 16, 19, 40).

Age

Mellemkjaer and colleagues described little difference in second primary melanoma incidence between premenopausal (≤ 45 years) (SIR 1.28; 1.10 – 1.47), perimenopausal (46-55 years) (SIR 1.37; 1.22-1.52) and postmenopausal (56 and above years) (SIR 1.26; 1.17 – 1.37) patients with breast carcinoma (40).

A study using the United States Surveillance, Epidemiology and End Results Program (SEER) registry of 40,819 female breast cancer survivors between 1991 and 1993 reported that risk of melanoma remained higher for younger (20-49 years; relative risk (RR) of 1.9) than older (65+ years; RR of 1) patients when compared to the general population (32).

A higher risk for younger patients corroborates with SEER registry findings from Goggins et al., who reported a higher melanoma risk for patients 50 years or below at the diagnosis of breast cancer (SIR = 1.46) compared to above 50 years (SIR = 1.07) (16). Similarly, Yang and colleagues found a relative risk of 1.38 for those below the age of 45 compared to 1.12 for those above the age of 45 (41).

In contrast, a European hospital-based study in 2018 found that age at the diagnosis of breast cancer is associated with the risk of melanoma. When accounting for 21,527 females with primary breast cancer at the European Institute of Oncology, melanoma SIR of melanoma increased from 1.98 to 2.71 when accounting for those only over the age of 70 at diagnosis and decreased to 1.00 for those below the age of 50 (26). In this study, aside from age at breast cancer diagnosis, no other single factor was associated with the risk of melanoma (26).

Taken together, these findings of these studies yield much conflicting evidence and indicate that the role of age in the risk of melanoma after breast cancer must continue to be investigated.

Radiation and chemotherapy

Goggins et al. noted a 42% increased risk of melanoma among patient with breast cancer who underwent radiation therapy (16). An increased incidence of melanoma following radiation therapy in patients with breast carcinoma was consistent with the findings of an institutional case series of 1,884 patients where a SIR of 2.5 was reported (28). However, some studies could not find an association between radiotherapy and melanoma occurrence (29, 42). They found positive associations for radiotherapy and breast cancer as well as gynaecological cancers and leukaemia (29). Similarly, while a study observed an increased hazard ratio of melanoma associated with chemotherapy among breast cancer patients over 50 years of age (18), others have noted only positive, yet insignificant findings (34) and even no increase in risk with chemotherapy (29).

Gender

Auvinen et al. assessed the risk of subsequent cancers amongst 1788 men with breast cancer from the SEER registry (43). Aside from the strongly elevated risk in developing contralateral second breast cancer (SIR = 29.65; 15.48-52.41), these patients also had an increased risk of melanoma (SIR=2.41; 1.15-4.43) (43). Interestingly, a retrospective registry-based cohort study by Satram-Hoang and colleagues indicated that the increased risk of melanoma for male patients with breast cancer was high among older men (70+ years) and in non-Hispanic whites (44).

3.3 Second Primary Cancers Following Melanoma

Caini et al. conducted a meta-analysis that included twenty-three independent research publications and over 350,000 patients with melanoma (10). The risk of second primary cancer was found to be increased when it included the risk of second primary melanoma cases (SRR 1.57; 1.29-1.90). The cancers include cancers of soft tissue (SRR 6.80; 1.29- 35.98), non-melanoma skin (SRR 4.01; 1.81-8.87), bone (SRR 2.09; 1.08 – 4.05), non-Hodgkin-lymphoma (SRR 1.37; 1.22-1.54), kidney (SRR 1.34; 1.23-1.45), prostate (SRR 1.25; 1.13-1.37), female breast (SRR 1.14; 1.07-1.22) and colorectum (SRR 1.12; 1.00-1.25) (10). Findings were explained by the tendency for some known and possibly unknown exposures to co-occur, a possible genetic predisposition and a level of diagnostic anticipation for second primary malignancies in melanoma survivors (10).

3.4 Breast cancer following melanoma

Standardised incidence ratio (SIR) ranged from 1.03 to 4.10 for primary breast carcinoma after cutaneous melanoma (Figure 2)(Table 3). Caini et al. evaluated the incidence of second primary cancer among 1537 melanoma patients from Northern Italy (14). Among the SPCs, the most significantly raised SIR was noted to be for breast cancers compared to other cancers (SIR 4.10; 2.79-6.03) (14). No significant difference was noted for melanomas with different histological characteristics or by the exclusion of in situ melanoma (14). However, a more recent study by Kimlin et al. of patients with an in-situ melanoma using the Queensland Cancer Registry in Australia found no increase in risk for a second primary cancer (SIR 0.97; 0.95-1.00) including breast cancer (SIR 1.03; 0.95-1.13) (45). This study corroborates with Balamurugan et al. who used data from the SEER program in the United States from 1996 to 2006 to calculate which found a non-significant elevation in SIR of 1.05 for breast cancers (46).

Despite a non-significant elevation for melanoma in situ, invasive melanomas carried a significant SIR of 1.18 for subsequent breast cancer diagnosis compared to the general population (46). Among women diagnosed with invasive melanoma, SIR was most increased for those followed-up with breast cancer within the first month of diagnosis (SIR 1.76) compared to those diagnosed after 120 months (SIR 0.96). The diagnosis of breast cancer early in follow up is in line with previous findings made by Goggins et al. who only found a significant risk for those diagnosed with breast cancer less than three months following melanoma (SIR 1.25; 1.09-1.42) (16). Similarly, while Møller et al. established a significant excess in risk for breast cancer incidence following melanoma diagnosis (SIR 1.19; 1.13-1.26), this risk was highest for those diagnosed with breast cancer within a year of melanoma diagnosis (SIR 1.40; 1.18-1.65) compared to those diagnosed after ten years or more (SIR 1.10; 1.00-1.21) (40). Breast cancer occurrence within a year of melanoma diagnosis suggests the possibility of screening bias. Compared to these studies (16, 40), other studies have noted similar levels of risk across follow-up periods (8). The role of genetic or non-genetic factors in the pathogenesis of second primary breast cancer is supported by the diagnosis of melanoma at or below the age of 50 having a higher excess risk (SIR 1.19; 1.04-1.35) compared to patients over the age of 50 (SIR 1.07; 0.98-1.17) for female breast cancer (16).

3.5 Associated Factors

A bi-direction association exists between melanoma and breast cancer occurrences (14). Possible causes of the association have been explored in literature including genetics, biological factors and the role of surveillance bias.

3.5.1 Genetics

Investigations into inherited germline mutations have highlighted a possible genetic relationship between melanoma and breast carcinoma. While familial germline mutations account for only a small fraction of cancers observed in the general population, increasing genetic evidence coupled with positive epidemiological findings is suggestive of a shared aetiological mechanism that underlies both breast carcinoma and melanoma. Previous studies have confirmed the role of *BRCA2* and *CDKN2A* germline mutations, respectively, in the pathogenesis of patients with breast carcinoma (47-54) and cutaneous melanomas (55-60). The study will also discuss *CDK4* and *BAP1*, two genes associated with cutaneous melanoma but where a relationship with breast cancer remains largely unexplored (61).

BRCA2

BRCA2 is a tumour suppressor gene which controls and suppresses cell proliferation to prevent tumour development (39). For germline *BRCA2* mutation carriers, retrospective studies estimate risk for breast cancer to age 70 years that range from 27-84% (47-54). In 2017, Kuchenbaecker et al. carried out a prospective cohort study on 3,820 *BRCA2* mutation carriers and noted that the cumulative risk of breast cancer risk at 80 years old was 69% (62). After examining 3,728 individuals from 173 breast-ovarian cancer families collected within 20 different centres in Europe, USA and Canada, The Breast Cancer Linkage Consortium (BCLC) reported that *BRCA2* mutation carriers had increased risks of several cancers including melanoma (RR = 2.58; 1.28-5.17) (63). No cases of melanoma occurred in carriers older than 65 years, suggesting that age may be a critical deciding factor (63). Validating BCLC's findings, *BRCA2* mutation carriers have shown an increased risk for melanoma in several other familial studies suggesting the possibility of a genetically plausible association between breast

carcinoma and melanoma (64, 65). Utilising genetic testing or pedigree analysis to detect carriers, Moran et al. noted a 2.7-fold increase in melanoma risk compared to the general population for patients positive for *BRCA2* mutation (64). In addition, Johannsson and colleagues noted a similar but non-significant 2.7 fold increase in melanoma risk in patients with a *BRCA2* mutation (65). The non-significant finding in this study ($p > 0.05$) might be attributed to the smaller sample size. In contrast, one retrospective cohort study failed to show an association between *BRCA2* mutation and melanoma (66). Furthermore, a study of 139 Dutch families even found a significantly decreased relative risk ($RR = 0.1$) of melanoma in mutation carrier when compared with Dutch's general population cancer incidence rates (67).

Variation in findings raises questions regarding the limitations of large familial studies. Limitations include selection bias that may overestimate cancer risk in mutation carriers, not genetically testing all patients in *BRCA2* carrier cohorts, lack of pathological or clinical confirmation of all melanoma cases and calculation of relative risk and confidence intervals based on fewer than ten instances of observed melanoma (68).

Studies directly determining the impact of *BRCA2* mutation on melanoma risk may provide additional insight into a clinical association. Debnaik et al. conducted a large case-control study comparing the prevalence of three common *BRCA2* mutations between 627 unselected Polish patients with melanoma and 3800 healthy controls (69). Prevalence of *BRCA2-N991D* variant was significantly higher in the cases versus control groups ($OR = 1.8$; $1.3-2.4$), while the prevalence of the two other *BRCA2* variants (T1915M and N372H) remained non-significant (69).

Several smaller studies have yielded contrasting findings regarding a *BRCA2* related association between breast carcinoma and melanoma. In a case study including three families with a history of both breast carcinoma and melanoma, no *BRCA2* mutation was found (70). Similarly, despite experiencing an increase in breast cancer risk, no *BRCA2* mutations were

detected amongst malignant melanoma patients and their relatives from families with strong cancer aggregation (71). Another study only noted one *BRCA2* mutation amongst 96 early-onset malignant melanoma families and one amongst 30 families with an aggregation of malignant melanoma and breast cancer (72). Taken together, the uncommon finding of *BRCA2* mutation does not exclude a link between *BRCA2* and melanoma. Instead, it suggests that the gene may be only partly responsible for an association between breast and melanoma cancers.

CDKN2A

CDKN2A is considered a tumour suppressor gene involved in the pathogenesis of melanoma (73). *CDKN2A* is responsible for the production of several tumour suppressor proteins, including p16(INK4A) and p14(ARF) (74). While p16(INK4A) blocks the ability of CDK4 and CDK6 to stimulate cell cycle progression, p14(ARF) functions to protect p53 from being broken down (74). *CDKN2A* mutation is well-known to be susceptible to melanoma. Approximately 5-10% of cutaneous melanomas are reported to be familial (75). *CDKN2A* mutation is prevalent among 20-40% of these familial cutaneous melanoma cases (76). At the age of 80, the risk of melanoma in *CDKN2A* mutation carriers is reported to be 28% (60). A similar association between *CDKN2A* mutation and breast carcinoma may be responsible for a second primary cancer relationship. A Swedish study noted a high frequency of breast cancer in patients with *CDKN2A* 113insArg mutations (77). Genotyping of 4,209 cases of breast cancer in Poland found the *A148T* variant to be overrepresented compared to 3,000 controls (58). The strongest association was for patients diagnosed with breast cancer at age 30 or under (OR= 3.8; p=0.0002). The association of *A148T* variant in *CDKN2A* was also commonly noticed with patients with breast cancer who are at or below 50 years of age (OR= 1.5; p=0.002). All these findings concur with the notion that *CDKN2A* is also a breast cancer susceptibility gene (58).

Moreover, previous studies have demonstrated conclusive evidence indicating the occurrence of breast cancer at levels higher than baseline in melanoma families with truncating *CDKN2A* mutations (56, 57). However, few studies since have been able to establish such an association between *CDKN2A* mutations and breast cancer (78-80). Such discrepancy implies the need for more extensively controlled studies of different populations to precisely determine the association, particularly when not all populations harbour mutation carriers at the same frequency and that different mutations may be associated with different cancer risks.

BAP1

BAP1, a known tumour suppressor gene, encodes a deubiquitinating enzyme and regulates key cellular pathways including cell cycle control, cellular differentiation and DNA damage repair (81). Germline mutations in *BAP1* give rise to BAP1-Tumour Predisposition Syndrome - characterised by an increased risk for uveal melanoma, malignant mesothelioma, cutaneous melanoma and renal cell carcinoma (82, 83). Data collated by Haugh et al. found that of 215 patients from 87 families with germline *BAP1* mutation, the most prevalent malignancies were uveal melanoma (n=60; 28%), mesothelioma (n=48; 22%), cutaneous melanoma (n=38; 18%) and renal cell carcinoma (n=20; 9%) (84). However, a number of other malignancies were also reported, including breast cancer, suggesting the full spectrum of the syndrome is yet to be elucidated. Paradoxically, for cutaneous melanomas, BAP1 overexpression promotes cell growth while BAP1 knockdown suppresses cell proliferation through a concomitant decrease in survivin - a known anti-apoptotic factor in melanoma (85). However, in breast cancers, the pathogenic role of *BAP1* remains unclear. The gene is located in the 3p21 chromosomal region, an area commonly deleted in breast cancer patients (86). Early studies have suggested that *BAP1* enhances BRCA1-mediated inhibition of cell growth in breast cancer cells (87). Current literature indicates the prevalence of *BAP1* mutation is rare amongst the general population. In a

population-based analysis of 1977 sporadic cutaneous melanoma cases, less than 1% carried a germline mutation of *BAP1* (88). Somatic *BAP1* mutations are identified in 2.5-5% of primary, non-desmoplastic melanomas, 2.5%-22% of desmoplastic melanomas and 9% of metastatic melanomas (89-91). For breast cancer, biallelic inactivation of *BAP1* was noted to be rare (0.4%) in an analysis of 760 cases (92) and somatic mutations are also reported to be uncommon (1.8%) (93). Taken together, the low frequency of *BAP1* mutation implies a minimal pathogenic significance for *BAP1* among patients with cutaneous melanoma and second breast cancers. Regardless, continued investigation of *BAP1* through clinical, epidemiological and functional studies are required to better understand its role in these tumourigenic associations and the variety of cancers involved in its syndrome.

CDK4

Germline mutations in tumour suppressor gene *CDK4* prevent the normal physiological inhibition of p16(INK4A) protein leading to cell cycle progression (61). *CDK4* has been identified as a high-risk susceptibility gene for cutaneous melanoma (94). However, the total number of familial melanoma pedigrees with *CDK4* germline mutations are scarce in the literature. In the largest familial study of *CDK4* germline mutation to date (17 families from eight countries), the *CDK4* mutation penetrance at age 50 was 74.2% with all mutations, either a Arg24His or Arg24Cys substitution on exon 2 (95). However, *CDK4* germline mutations are scarce with the literature recording only 17 melanoma families affected (76). Literature examining the association between *CDK4* and breast cancer is limited, primarily due to the rarity of the mutation. Indeed, the GENIE database suggests that *CDK4* mutations are only present in 0.23% of all breast carcinoma patients (96). To best of our knowledge, only one case-control study of 200 breast cancer patients and 200 healthy controls has reported on *CDK4* associated breast cancer risk (97). No mutations were found in the melanoma-associated exon 2,

despite a significant increase in risk associated with a 5732 G>A substitution in intron 4 (OR=5.05; 95% CI = 2.17-11.78) (97). With *CDK4* mutation already fielding a limited role in the incidence of both breast and melanoma cancers, a study by Monnerat et al. points further to the unlikelihood that *CDK4* mutation is responsible for the melanoma-breast cancer association (55). In this study of 82 patients with a history of both breast carcinoma and cutaneous melanoma, no *CDK4* (exon 2) germline mutations were found (55). The identification of two *BRCA2* and two *CDKNA* germline mutations in this study further suggests that other factors aside from genetics chiefly contribute to the association between the two cancers.

3.5.2 Biological Factors - Oestrogen receptors

Increased oestrogen exposure is considered as a risk factor for many cancers, including breast, colorectal, endometrial and ovarian cancers (98). Oestrogens bind to oestrogen receptors (ER) and have a proliferative effect on epithelial tissue that increases the chance for random genetic errors (99). A role of oestrogen in melanoma progression could rationalise an association between breast carcinoma and melanoma. Despite its oncogenic role in many cancers, the role of oestrogen in melanoma progression has remained controversial since the discovery of its receptors on melanoma tissue (100). Oestrogen receptor alpha (ER α) and oestrogen beta (ER β), two different forms of ER, are nuclear receptors found on skin tissue and are responsible for mediating the cellular effects of oestrogen (101). ER β often functions as a protective receptor by counteracting the proliferative function of ER α via antagonising ER α target genes and through inducing the transcription of anti-proliferative ER β target genes (102).

A study by de Giorgi et al. on 66 malignant melanocytic lesions found that ER β protein expression was inversely associated with Breslow thickness (a measure of the deepest component of the melanoma) and was significantly downregulated in the healthy and melanoma tissue of male patients (103). In another study, de Giorgi and colleagues reported markedly

decreased expression of ER β during the metastatic phase of melanoma by analysing a small group of patients (14 patients, including two melanocytic nevi) (104). These studies suggest that loss of ER β expression may be a significant step in decreasing the antagonising action of ER β on ER α -controlled malignant melanocyte proliferation (102).

The epidemiological association between exogenous oestrogens and the development of melanoma in premenopausal women using oral contraceptives remains controversial. A meta-analysis conducted by Gandini et al. summarising a total of 5,626 melanoma cases from 36 observational studies found no increase in the risk of melanoma with the use of oral contraceptives and hormonal therapy (105). Two previous studies with meta-analyses and a pooled analysis of ten case-control studies have also found that oral contraceptives do not influence the incidence of melanoma in premenopausal women (106-108). Few studies have shown an effect of hormone therapy in increasing the risk of melanoma in postmenopausal women (109, 110). A population-based case-control study by Koomen et al. noted that women who used oestrogens for more than half a year were approximately 40% more likely to develop melanoma than women who did not use oestrogen or for less than half a year (adjusted OR = 1.42; 1.19-1.70) (111). Koomen et al. recommend further prospective randomised studies, including questions on possible confounders such as drug use and sun exposure (111). Overall, additional experimental research attempting to elucidate the effects of oestrogen on the development and progression of cutaneous melanoma is required.

3.5.3 Surveillance Bias

Socio-cultural factors may be a potential cause for the bi-directional association between melanoma and breast carcinoma. Both melanoma and breast carcinoma increase in incidence in populations with a higher level of socio-economic status, possibly due to compliance with cancer screening and knowledge of cancer risk factors (112, 113). Moreover, the diagnosis of

malignancy for a patient leads to hospital visits, medical imaging and laboratory tests during treatment and follow-up that provide an opportunity for the screening and diagnosis of second cancers. Patients with cancer are also better educated and are more proactive to report signs and symptoms promptly to their doctors. High rates of screening, medical imaging and hospital visits potentially lead to the early diagnosis of slow-developing cancers such as some subtypes of breast carcinomas (114). Lending to the significance of surveillance bias, the 2016 study by Caini et al. found that diagnosis of second primary cancer was common among patients having melanoma within two years of their initial diagnosis (10).

4.0 Conclusion

This study showed a significant association between breast cancer and melanoma incidence and was related to various epidemiological, genetic and biological factors. While many registry-based and hospital-based studies have indicated a significant increase in standardised incidence ratios (SIRs) for these malignancies, the results remain inconclusive. Some studies found little or no significant increase in the risk of these co-occurring cancers and attributed the rise to surveillance bias. Younger age may be a possible risk factor for second primary cancer as well as radiation after a breast cancer diagnosis. The positive breast carcinoma – melanoma associations, could be attributed to more common tumour susceptibility genes such as BRCA2 and CDK2NA or biological factors such as oestrogen exposure. To improve understanding of the clinical correlation between the breast carcinoma and melanoma association, further research using more comprehensive population-based epidemiological studies in conjunction with investigations into the influence of genetic and biological influences is warranted.

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Author contributions

AJ and VG were involved in project design, analysis and making structural frameworks. AJ has led the quantitative analysis and writing. TC and AL have made contributions in proofreading and correcting the clinical aspects of melanoma and breast carcinomas. VG has supervised AJ in methodology development and writing.

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Risk Factors	
BREAST CARCINOMA	CUTANEOUS MELANOMA
Women gender	Male gender
Increasing age	Increasing age
Family history of breast carcinoma	Family history of melanoma
Diagnosis of atypical hyperplasia or lobular carcinoma in situ	Unusual melanocytic lesions (atypical moles)
Previous history of breast carcinoma	Previous history of non-melanoma skin carcinomas or melanoma
BRCA1 or BRCA2 gene mutation for familial cancer	CDKN2A mutation for familial melanoma
Endogenous oestrogen exposure	Ultraviolet light exposure
Hormonal factors	Fair skin, freckling and light hair

Table 1: Comparison of risk factors between patients with breast carcinoma and cutaneous melanoma

Author, Year	Location	Date Range	Sample Description	Number of Melanoma	SIR
Harvey, 1985	Connecticut Tumor Registry, USA	1935 to 1982	41,109 women with primary breast carcinoma	668	1.5
Volk, 1997	Cancer Registry of Slovenia	1961 to 1985	8,917 women with primary breast carcinoma	15	2.7 (1.5-4.4)
Rubino, 2000	Institute Gustave Roussy, France	1973 to 1992	4,416 female one-year breast carcinoma survivors	10	2.7 (1.4-4.8)
Levi, 2003	Swiss Cancer Registry	1974 to 1998	9,729 women with primary breast carcinoma	25	1.41 (0.91-2.09)
Goggins, 2004	Surveillance, Epidemiology, and End Results (SEER), USA	1973 to 1999	668 women with melanoma after breast carcinoma	NR	1.16 (1.09-1.27)
Mellemkjaer, 2006	Cancer Registries from Europe, Canada, Australia and Singapore	1943 to 2000	525,527 women with primary breast carcinoma	1,135	1.29
Mellemkjaer, 2006	Cancer Registries from Europe, Canada, Australia and Singapore	1943 to 2000	525,527 women with primary breast carcinoma	1,135	1.29
Satram-Hoang, 2007	California Cancer Registry, USA	1988 to 2003	1,454 men ages 85 years or younger with primary breast carcinoma	14	2.98 (1.63 - 5.00)
Schaapveld, 2008	Dutch Population (North-Western and South-Eastern)	1989 to 2003	58,068 women with primary breast carcinoma	164	1.69 (1.44-1.97)
Kirova, 2008	Curie Institute, France	1981 to 1997	16,705 women with primary BC	37	1.07 (0.76-1.48)
Stracci, 2009	Umbrian Population Cancer Registry, Italy	1994 to 2006	7,840 women with primary breast carcinoma	16	2.24 (1.14-3.34)
Cortesi, 2009	Modena Cancer Registry, Italy	NR	7,512 women with primary breast carcinoma	NR	2.25 (1.23-3.77)
Yang, 2011	Surveillance, Epidemiology, and End Results (SEER), USA	1988 to 2007	680 women with melanoma after breast carcinoma	90 and 590	Relative Risk for melanoma (Age <45y) = 1.38 (1.11-180)

					Relative Risk for melanoma (Age $\geq$ 45y) = 1.12 (1.03-1.21)
Coyte, 2014	West of Scotland Population, UK	2000 to 2004	8,386 women with primary breast carcinoma	17	1.64 (0.96 – 2.63)
Ricceri, 2015	European Cohort (EPIC)	1992 to 1998	10,045 women with primary breast carcinoma	27	2.12 (1.63-2.70)
Caini, 2016	European Institute of Oncology, Italy	2000 to 2010	25,613 women with primary breast carcinoma	52	5.13 (3.91 – 6.73)
Corso, 2018	European Institute of Oncology, Italy	1994 to 2010	21,527 women with primary breast carcinoma	59	1.98 (1.52 - 2.53)

Table 2: Studies investigating the risk of cutaneous melanoma after breast carcinoma diagnosis

Author, Year	Cohort/Sample	Date Range	Sample Description	Breast Cancer Incidence	SIR
Wassberg, 1999	Swedish Cancer Register	1958 to 1992	3,766 patients with a diagnosis of cutaneous melanoma in situ	33	SIR for breast carcinoma for patients with cutaneous melanoma in situ= 1.4 (1.0-1.9)
Wassberg, 1999	Swedish Cancer Register	1958 to 1988	20,354 patients with a diagnosis of cutaneous melanoma	151	SIR for breast carcinoma for patients with cutaneous melanoma = 1.02 (0.87-1.20)
Schmid-Wendtner, 2001	Department of Dermatology and Allergology, Germany	1997 to 1992	2,514 women with melanoma	32	1.1 (0.8-1.6)
Goggins, 2004	Surveillance, Epidemiology, and End Results (SEER), USA	1973 to 1999	721 women with BC after melanoma	721	1.11(1.03-1.19)
Mellemkjaer, 2006	Cancer Registries from Europe, Canada, Australia and Singapore	1943 to 2000	1,353 patients with melanoma after diagnosis of breast carcinoma	1,353	1.19 (1.13-1.26)
Levi, 2008	Swiss Cancer Registry	1974 to 2005	3,346 melanoma patients	39	1.04 (0.74-1.42)
Crocetti, 2008	Italian Network of Cancer Registry	1985 to 2002	14,560 melanoma patients	112	1.21
Spanogle, 2010	Surveillance, Epidemiology, and End Results (SEER), USA	1973 to 2003	151,996 patients with melanoma	1,565	1.07 (1.02-1.12)
Bradford, 2010	Surveillance, Epidemiology, and End Results (SEER), USA	1973 to 2006	89,515 melanoma patients who survived at least 2 months	1,256	1.10 (1.04-1.16)
Balamurugan, 2011	Surveillance, Epidemiology, and End Results (SEER), USA	1992 to 2006	40,881 patients with melanoma in situ, 76,041 patients with melanoma	335 in situ melanoma	SIR for breast carcinoma for in situ melanoma survivors = 1.05

				613 melanoma	SIR for breast carcinoma for melanoma survivors = 1.18 (statistically significant)
Jung, 2014	Alberta Cancer Registry, USA	1979 to 2009	6884 patients with cutaneous melanoma	67	SIR for breast carcinoma for cutaneous melanoma survivors = 1.1 (0.9-1.4)
Caini, 2016	European Institute of Oncology, Italy	2000 to 2010	1,537 patients with melanoma	26	4.10 (2.79-6.03)
Farr, 2017	Surveillance, Epidemiology, and End Results (SEER), USA	NR	464 males with second primary breast cancer after melanoma	464	1.26 (0.80 - 1.89)
Kimlin, 2018	Queensland Cancer Registry, Australia	1982 to 2012	4,917 patients with melanoma in situ	493	1.03 (0.95-1.13)

Table 3: Studies investigating the risk of breast carcinoma after a cutaneous melanoma diagnosis

Figure legends

Figure 1: Standardised incidence ratios of cutaneous melanoma after breast carcinoma diagnosis. Registry-based and hospital-based studies have concluded standardised incidence ratios (SIRs) ranging from 1.16 to 5.13.

Figure 2: Standardised incidence ratios of breast carcinoma after cutaneous melanoma diagnosis. Standardised incidence ratio (SIR) ranged from 1.03 to 4.10 for primary breast carcinoma after cutaneous melanoma.