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Skin cancer risk in *BRCA1/2* mutation carriers*

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Summary

Women with *BRCA1/2* mutations have an elevated risk of breast and ovarian cancer. These patients and their clinicians are often concerned about their risk for other cancers, including skin cancer. Research evaluating the association between *BRCA1/2* mutations and skin cancer is limited and has produced inconsistent results. Herein, we review the current literature on the risk of melanoma and nonmelanoma skin cancers in *BRCA1/2* mutation carriers. No studies have shown a statistically significant risk of melanoma in *BRCA1* families. *BRCA2* mutations have been linked to melanoma in large breast and ovarian cancer families, though a statistically significant elevated risk was reported in only one study. Five additional studies have shown some association between *BRCA2* mutations and melanoma, while four studies did not find any association. With respect to nonmelanoma skin cancers, studies have produced conflicting results. Given the current state of medical knowledge, there is insufficient evidence to warrant increased skin cancer surveillance of patients with a confirmed *BRCA1/2* mutation or a family history of a *BRCA1/2* mutation, in the absence of standard risk factors. Nonetheless, suspected *BRCA1/2* mutation carriers should be counselled about skin cancer risks and may benefit from yearly full skin examinations.

Patients with a *BRCA1/2* mutation and their treating physicians are often concerned about their risk of developing other cancers, including skin cancer. While *BRCA1/2* mutation carriers have a well-documented risk of breast and ovarian cancer, their risk of cancers at other sites is less clear. Studies evaluating the association between *BRCA1/2* mutations and skin cancer are limited and have produced inconsistent results. The aim of this review is to provide clinicians with an overview of the current literature on the risk of melanoma and nonmelanoma skin cancers in *BRCA1/2* mutation carriers to aid clinical decision-making regarding skin cancer screening.

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The *BRCA1/2* genes

BRCA1 (chromosome 17) and *BRCA2* (chromosome 13) belong to a class of tumour suppressor genes that preserve chromosomal stability.[1] *BRCA1/2* genes play a critical role in the cellular response to double-stranded DNA breaks.[2–7] *BRCA1* is required for activation of S- and G2/M- phase cell-cycle arrest after DNA damage.[8] It also interacts with multiple DNA repair proteins such as RAD51, the RAD50/MRE11/Nibrin complex, Bloom's helicase and the Fanconi D2 protein. Through these interactions, *BRCA1* has roles in transcriptional regulation, ubiquitylation and chromatin remodelling.[9] The primary role of *BRCA2* is to regulate RAD51 filament formation and activity, a key enzyme in homologous recombination.[10]

Cells lacking *BRCA1* and/or *BRCA2* are unable to repair double-stranded DNA breaks by homologous recombination.[1,3–7] Double-stranded DNA breaks are normally repaired in three ways: nonhomologous end joining, single-strand annealing and homologous recombination. The first two pathways are error-prone, while the latter pathway is relatively error-free. When cells are *BRCA1/2* mutant, they are unable to perform homologous recombination, and DNA repair is pushed towards more error-prone pathways. Consequently, *BRCA1/2* mutant cells may gain additional genetic mutations during DNA repair and can develop chromosomal aberrations during cellular replication.[9] Many of these genetic mutations result in cell death, though some mutant daughter cells may survive and develop into a cell clone with malignant potential.[11]

As tumour suppressors, *BRCA1/2* genes play an essential role in preserving chromosomal structures and maintaining genomic stability.[1] In a given germline, a single defective copy of *BRCA1* or *BRCA2* is sufficient to increase the risk of carcinogenesis; the second copy is frequently lost in tumour cells. Somatic *BRCA1/2* mutations are uncommon in tumours arising in patients lacking *BRCA1/2* germline mutations; however, when present, the somatic alterations in these tumours can include promoter hypermethylation or loss of heterozygosity. [1,12,13]

The frequency of *BRCA1* or *BRCA2* mutations in the non-Ashkenazi U.S. population is estimated to be between 1 in 300 and 1 in 500, based on a series of validated models.[14–16] When prevalence estimates of *BRCA* mutations are restricted to populations of only European ancestry, the prevalence is approximately 0·25%. When further restricted to Ashkenazi Jews, the prevalence increases by a factor of 10–2·5%.[17–19]

There is a well-established association between *BRCA1/2* mutations and breast and ovarian cancer. Between 5% and 10% of cases of breast cancer in the U.S.A. are attributed to *BRCA* mutations, with varying risk between racial and ethnic groups.[20,21] The average cumulative risk of breast cancer in *BRCA1/2* mutation carriers is approximately 55–70%.[22] The risk of ovarian cancer in *BRCA1/2* mutation carriers ranges from 20% to 40%.[15] Pancreatic and prostate cancers have also been linked to *BRCA1/2* mutations.[17,23,24] For all these cancers, the strength of association is higher in founder ancestries, e.g. Ashkenazi Jewish, Icelandic and Finnish.[25–27] The risk of other cancers in *BRCA1/2* mutation carriers is less clear.

The risk of skin cancer in *BRCA1/2* carriers

Few studies have investigated the incidence of *BRCA1/2* mutations in patients with melanoma and nonmelanoma skin cancers. Currently, no genome-wide association study or exome studies have implicated *BRCA* single nucleotide polymorphisms (SNPs) or SNPs in linkage disequilibrium with the *BRCA* genes in the development of basal cell carcinoma, squamous cell carcinoma or melanoma. Much of the research on *BRCA1/2* mutations and skin cancer comes from large retrospective cohort studies evaluating the risk of various cancers, including skin cancer, in large families with *BRCA1/2* mutations. A major limitation of these studies is that none were conducted exclusively in genetically tested carriers. In most studies, risk of skin cancer was determined in individuals *at high risk of carrying a* BRCA1/2 *germline mutation* based on several criteria, including: (i) breast cancer diagnosis before age 60; (ii) breast cancer diagnosis in a male; (iii) ovarian cancer diagnosis at any age; (iv) known carrier status by genetic typing; (v) obligate carrier status based on pedigree analysis or (vi) a first degree relative of individuals in any previous category. Most studies did not specify how many individuals were confirmed mutation carriers.

Given that not all study subjects were tested for *BRCA1/2* carriers, it is unclear whether any links to skin cancer found in these studies can be attributed to *BRCA1/2* mutations. Additionally, it is important to recognize that evaluating the association between a genetic mutation and a given phenotype is far more complex than simply determining the co-occurrence of two conditions. Numerous genetic and environmental variables can confound results. In particular, when examining the link between *BRCA1/2* mutations and skin cancer, results may be confounded by a *BRCA1/2*-independent association between skin cancer and breast or ovarian cancer. In addition, patients with excessive sun exposure may develop skin cancers independent of germline mutations (i.e. phenocopy). Nonetheless, these studies may provide insight into potential links between *BRCA1/2* mutations and skin cancer and may identify key areas for future research.

Nonmelanoma skin cancer

Few studies have evaluated the risk of nonmelanoma skin cancers in *BRCA1/2* mutation carriers (Table 1).[28–31] A large study of 1873 patients, conducted in Sweden by Johannsson *et al.*,[30] compared cancer incidence in both *BRCA1* and *BRCA2* families to incidence in the general population. Although this study did not find an increased risk of nonmelanoma skin cancers among *BRCA2* families, it did report an increased risk of invasive squamous cell carcinoma of the skin among men in *BRCA1* families [standardized morbidity ratio (SMR) = 6·02, 95% confidence interval (CI) 1·96–14·05, $P = 0·002$)].[30] While significant, the wide CIs in this subset analysis raise some concerns with the power of this study. Nevertheless, this clinical association is particularly interesting in light of recent research, suggesting that *BRCA1* may play a role in the molecular pathogenesis of squamous cell carcinoma.[31,32] Genetic aberrations comprised of ultraviolet-induced cyclobutane pyrimidine dimers are often present in squamous cell carcinoma. Interaction between *BRCA1* and p53 may play a role in the removal of these dimers during DNA repair.[31,32] These data suggest that a defect in *BRCA1* may lead to high rates of unrepaired DNA damage and predispose patients to squamous cell carcinoma. A smaller study by Shih *et al.*[29] also suggested an association

between *BRCA1/2* mutations and nonmelanoma skin cancers. The implications of this study, however, are unclear given its small sample size and poor patient selection criteria. In contrast, a study evaluating the relative risk (RR) of nonmelanoma skin cancers in 82 first-degree relatives of genetically tested *BRCA1* and *BRCA2* carriers compared with the general population demonstrated no increase in nonmelanoma skin cancer risk (standardized incidence ratio = 0, 95% CI 0–19·8).[28]

With respect to basal cell carcinoma in particular, one study demonstrated possible links to *BRCA1/2* mutations. Ginsburg *et al.*[31] followed 2729 women with confirmed *BRCA1* or *BRCA2* mutations for a mean of 5 years and assessed them for the development of melanoma and nonmelanoma skin cancers. Of note, cancer diagnoses were not confirmed histologically; they were based on patient questionnaires. This study demonstrated that *BRCA2* mutation carriers were more likely to develop a basal cell carcinoma compared with *BRCA1* mutation carriers (odds ratio = 1·97, 95% CI 1·20–3·24, $P = 0·007$). Skin cancer incidence in *BRCA1/2* mutation carriers was not compared with the general population. Nonetheless, the authors of this study concluded that patients with *BRCA2* mutations should be counselled on skin cancer risk and monitored at least yearly by a dermatologist.[31] Given the shortcomings in the design of this study however, it is difficult to determine whether any association exists between basal cell carcinoma and *BRCA1/2* mutations.

Taken together, these studies suggest that *BRCA1/2* mutations generally do not predispose patients to nonmelanoma skin cancers, although one study demonstrated that *BRCA1* mutations may be linked to squamous cell carcinoma in certain cases.[30] Additional studies are needed to explore this possible association.

Melanoma

The association between melanoma and *BRCA1/2* mutations has been more extensively studied. *BRCA1* mutations have not been significantly associated with melanoma in large retrospective familial studies (Table 2).[17,30,33–35] In contrast, suspected *BRCA2* mutation carriers have shown an increased risk of melanoma in several, but not all, studies (Table 3). The largest, most highly powered study evaluated 3728 individuals from breast–ovarian cancer families. This study demonstrated that suspected *BRCA2* mutation carriers were 2·5 times more likely to develop melanoma compared with the general population (RR = 2·58, 95% CI 1·28–5·17, $P = 0·01$).[23] Another study conducted by Moran *et al.*[35] also showed an increased risk of melanoma in suspected *BRCA2* mutation carriers; however, the statistical significance of this finding was not assessed. This study of 1526 individuals demonstrated a 2·7-fold increase in melanoma in patients who tested positive for a *BRCA2* mutation or were obligate carriers based on pedigree analysis when compared with the general population (RR = 2·695, 95% CI 1·0–5·7).[35] A third study of 728 individuals, by Johannsson *et al.*,[30] assessed the risk of melanoma in *BRCA2* families as a whole, including mutation carriers and noncarriers, compared with the general population. Similar to Moran *et al.*,[35] this study found a 2·7-fold increase in melanoma risk in *BRCA2* families (SMR = 2·71, 95% CI 0·56–7·92, $P = 0·101$).[30] In this study, the nonsignificant *P*-value may have been due to a much smaller sample size.

Several studies, however, have failed to show an association between *BRCA2* mutations and melanoma. Two large *BRCA2* breast cancer families had no cases of melanoma among *BRCA2* carriers, although the expected number of melanoma cases in families of these sizes was only 0·17.[36] Another study of 139 Dutch families with *BRCA2* mutations found a markedly reduced relative risk (RR = 0·1) of melanoma when compared with Dutch cancer incidence rates. This study, however, was also underpowered.[37]

Overall, although large familial studies provide valuable insight into clinical associations, there are several limitations to this approach. Studies in large *BRCA1/2* families have been criticized for selection bias that may overestimate cancer risk in mutation carriers.[38–40] Furthermore, not all patients in the '*BRCA1/2* carrier' cohort were genetically tested, further confounding results. The second major limitation of these studies was that not all melanoma cases could be confirmed by pathology reports or clinical records. Cancer diagnoses in *BRCA1/2* families were based on a combination of patient history, ICD codes from medical records or census registries, and national cancer registries. Additionally, RR and 95% CI calculations were based on fewer than 10 observed cases of melanoma in all studies. Therefore, incorrectly reporting even a small number of melanoma cases could greatly alter results. Lastly, a history of breast cancer in a large number of study subjects is a major confounder. Several studies, which have not investigated *BRCA1/2* mutation status, have reported an association between breast cancer and melanoma with standardized incidence ratios ranging from 1·16 to 2·74.[41–50] Hence, melanoma and breast cancer may have a *BRCA1/2*-independent association, given the rare occurrence of *BRCA1/2* germline mutations in the nonfamilial setting.

In order to address the role of *BRCA1/2* in melanoma more directly, several studies have determined the occurrence of *BRCA1/2* mutations in patients with a history of melanoma (Table 4). Of note, several of these studies are underpowered and demonstrate large variability in terms of genetic mutations and ethnic populations being investigated. The largest of these studies compared the prevalence of three common *BRCA2* mutations in 627 unselected Polish melanoma patients to over 3800 healthy controls.[51] The prevalence of the *BRCA2-N991D* variant was significantly greater in melanoma patients compared with control subjects (odds ratio = 1·8, 95% CI 1·3–2·4, $P = 0·002$); the association between melanoma and the other *BRCA2* variants examined was not statistically significant. Another study demonstrated two *BRCA2* mutations in 557 Italian patients with melanoma, though the mutation variants in these cases were unknown.[52] Additionally, one study of European patients with primary breast cancer and melanoma, unselected for family history, identified three of 82 patients (3·7%) with deleterious *BRCA* mutations (one *BRCA2* and two *BRCA1*).[53] Six additional *BRCA1*/2 mutations of unknown significance were reported. The authors did not attribute *BRCA1* to melanoma risk in the two patients with deleterious mutations, due to their Fitzpatrick skin type and strong history of sun exposure. It is noteworthy that two cases of *BRCA2* mutations (one deleterious mutation, one unclassified variant) had concomitant *TP53* germline mutations. Current research has shown that disruption of the p53 pathway is crucial for the development of *BRCA1/2*-associated cancers.[54,55] Hence, the combination of germline *TP53* and *BRCA1/2* mutations may have played a role in melanoma formation in these cases. It should also be noted that germline *TP53* mutations are a feature of Li–Fraumeni syndrome. While cases of melanoma,

including multiple primary melanomas, have been reported in patients with this syndrome, the association of melanoma with Li–Fraumeni syndrome is controversial.[56]

In contrast, Landi *et al.*[57] screened three Italian families that had at least two relatives with melanoma and at least one relative with breast cancer for *BRCA2* mutations, as part of a larger familial melanoma study, and no *BRCA2* mutations were detected. Additionally, a study conducted in Israel that evaluated 92 melanoma patients for *BRCA2* Ashkenazi founder mutations also failed to identify any mutations.[38]

In summary, the evidence supporting an association between *BRCA1*/2 mutations and melanoma is not straightforward. While no studies have shown a statistically significant association between *BRCA1* mutations and melanoma, the studies investigating *BRCA2* mutations and melanoma have produced inconsistent conclusions. Despite some suggestive evidence of melanoma risk observed in suspected *BRCA2* mutation carriers in breast and ovarian cancer families, there are substantial study design shortcomings limiting the certainty of these conclusions. As genetic testing becomes less expensive, it is possible that more thoroughly designed studies can be undertaken.

To conclude, current data have not established strong links between *BRCA1*/2 mutations and skin cancer. There are no reported associations between *BRCA1* mutations and melanoma. With respect to *BRCA2*, studies in breast and ovarian cancer families have not conclusively identified an increase in melanoma risk among suspected carriers. Additional, more definitive studies are needed. There are no established guidelines for skin cancer screening in *BRCA1*/2 mutation carriers. Given the current state of medical knowledge, there is insufficient evidence to warrant increased surveillance of patients with a confirmed *BRCA1*/2 mutation or a family history of a *BRCA1*/2 mutation, in the absence of standard skin cancer risk factors. Nonetheless, suspected *BRCA1*/2 mutation carriers should be counselled about skin cancer risks and may benefit from yearly full skin examinations.

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What's already known about this topic?

- While *BRCA1/2* mutation carriers have a well-documented risk of breast and ovarian cancer, their risk of cancers at other sites is less clear.

What does this study add?

- Our review demonstrates there is inconclusive evidence to support a strong link between *BRCA1/2* mutations and skin cancer.
- Increased skin cancer surveillance in *BRCA1/2* mutation carriers is not recommended.

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Table 1

Studies evaluating the association between nonmelanoma skin cancers and *BRCA1/2* mutations

Study	Patient demographic	Study design	Method of obtaining cancer status	Interval of follow-up	Sample size of cohort	Results
Johannsson 1999[30]	Southern Sweden	Cohort pedigree analysis of large *BRCA1/2* families in which index cases were confirmed to have *BRCA1/2* mutations by genetic testing. Risk was assessed for the family as a whole, including mutation carriers and nonmutation carriers, though family branches that were proved or suspected of being noncarriers were excluded Control: compared with incidence in the general population	ICD-7 codes from the population-based Census Registry and the Swedish Cancer Registries	1958–1995	*BRCA1*: 1145; *BRCA2*: 728	Increased risk of squamous cell carcinoma reported in men from *BRCA1* families (n = 549, SMR = 6·02, 95% CI 1·96–14·05, P = 0·002) The risk of nonmelanoma skin cancers was not significantly elevated in women from *BRCA1* families (n = 596, SMR = 2·36, 95% CI 0·06–13·13, P = 0·346) There were no nonmelanoma skin cancers reported in *BRCA2* families
Ginsburg 2010[31]	North America, Europe and Israel	Women from *BRCA* families with a confirmed *BRCA1* or *BRCA2* mutation were prospectively followed and evaluated for the development of skin cancers for an average of 5 years. Skin cancer development in relatives of study subjects were analysed separately (results not included in chart)	Patient questionnaire. Categories included BCC, melanoma and skin cancer NOS. Results were not confirmed histologically	5 years (range 0–13·6 years)	*BRCA1*: 1779	Skin cancers at baseline and during follow-up period: BCC: 31 (1·74%) Melanoma: 23 (1·29%) Any skin cancer: 92 (5·2%)
					BRCA2: 950	Skin cancers at baseline and during follow-up period: BCC: 32 (3·37%) Melanoma: 14 (1·47%) Any skin cancer: 64 (6·7%)
Loman 2003[28]	Sweden	The risk of various cancers compared with the general population was assessed in first-degree relatives of a population-based set of index individuals with early-onset breast cancer. Subjects included women with a diagnosis of breast cancer at 41 or younger, a known family history of cancer and known *BRCA1* and *BRCA2* mutation status. Relatives of each group were analysed separately	National and regional cancer registries	1995–2000	First-degree relatives of confirmed *BRCA1/2* carriers: 82	Melanoma: SIR 2·8, 95% CI 0·70–15·6 Nonmelanoma: SIR 0, 95% CI 0–19·8
Shih 2000[29]	U.S.A.	Women ascertained from high-risk breast–ovarian cancer clinics with breast cancer reporting at least one other primary cancer in themselves or in a relative with breast cancer were compared with women with breast	Cancer diagnoses were based on patient history. Pathology reports were obtained on all probands and family	Cancers diagnosed at time of study. No follow-up period	Women with breast cancer only: 99 Women with breast cancer and at least one	16 patients with breast cancer also had a nonmelanoma skin cancer: 3/16 (18·8%) had a *BRCA1* mutation; 1/16 (6·2%) had a *BRCA2* mutation

Study	Patient demographic	Study design	Method of obtaining cancer status	Interval of follow-up	Sample size of cohort	Results
		cancer who reported a personal or family history of breast cancer only	members when possible		secondary cancer: 98	

SMR, standardized morbidity ratio; CI, confidence interval; BCC, basal cell carcinoma; NOS, not otherwise specified; SIR, standardized incidence ratio.

Table 2

Retrospective cohort studies evaluating the risk of cutaneous melanoma in *BRCA1* families

Study	Patient demographic	Study design	Method of obtaining cancer status	Follow-up	Sample size of cohort	RR	95% CI	*P*-value
Thompson 2002[34]	Western Europe and North America	Cohort: individuals from 699 *BRCA1* families ascertained by the Breast Cancer Linkage Consortium. Subjects included tested mutation carriers, patients with ovarian cancer, male patients with breast cancer, women diagnosed with breast cancer at < 60 years and first-degree relatives of individuals in any of these categories Control: compared with incidence in the general population	ICD codes from medical record. Histological confirmation was available for some but not all cases	1960–1999	11 847	1·11	0·58–2·15	0·7
Moran 2012[35]	North West and West Midlands of England	Cohort: patients in a *BRCA1* family who tested positive for a mutation or were obligate carriers based on pedigree analysis Control: compared with incidence in the general population	Cancer diagnosis obtained from patient history. All cancers confirmed by regional cancer registry	1975–2005	1815	0·9	0·1–3·1	NA
Johannsson 1999[30]	Southern Sweden	Cohort: pedigree analysis of large *BRCA1/2* families in which index cases were confirmed to have *BRCA1/2* mutations by genetic testing. Risk was assessed for the family as a whole, including mutation carriers and nonmutation carriers, though family branches that were proved or suspected of being noncarriers were excluded Control: compared with incidence in the general population	ICD-7 codes from the population-based Census Registry and the Swedish Cancer Registries	1958–1995	1145	1·23	0·15–4·43	0·68
Brose 2002[33]	Michigan and Pennsylvania, USA	Cohort: *BRCA1* mutation carriers in 147 families were identified in two academic breast and ovarian cancer risk evaluation clinics. *BRCA1* mutation carriers were identified either on the basis of direct genetic testing or as presumed carriers. Presumed carriers were defined as being in the line of descent between two tested mutation carriers or between a mutation carrier and an individual with breast or ovarian cancer Control: compared with incidence in the general population	Personal interview or mailed questionnaire	10 years: patients recruited from 1991 to 1994	483	2·5[a]	1·1–3·9	NA

RR, relative risk; CI, confidence interval; NA, not available.

[a]This is the cumulative age adjusted risk. The RR was not calculated.

Table 3

Retrospective cohort studies evaluating the risk of cutaneous melanoma in *BRCA2* families

Study	Patient demographic	Study design	Method of obtaining cancer status	Interval of follow-up	Sample size of cohort	RR	95% CI	*P*-value
Breast Cancer Linkage Consortium 1999[23]	Europe and North America	Cohort: patients with breast cancer at < 60 years, ovarian cancer or male breast cancer and known carriers by typing and obligate carriers Control: compared with incidence in the general population	ICD codes from medical records. 48% of diagnoses confirmed by pathology report, clinical records, or death certificate	1960–1995	3728	2·58	1·28–5·17	0·01
van Asperen 2005[37]	Netherlands	Cohort: men and women from 139 *BRCA2* families with 66 different pathogenic mutations. To avoid testing bias, chose not to estimate risk in typed carriers, but rather in male and female family members with a 50% probability of being a carrier Control: compared with incidence in the general population	Mentioned by individual or family member during genetic counselling meeting. Cancer diagnoses were medically and/or pathologically confirmed by pathology reports and clinical records	1960 to date of first cancer diagnosis, death, last contact, last DNA test in the family or age 80	1811	0·1	0·01–0·2	NA
Moran 2012[35]	North West and West Midlands of England	Cohort: patients who tested positive for a mutation or were obligate carriers based on pedigree analysis Control: compared with incidence in the general population	Cancer diagnosis obtained from patient history. All cancers confirmed by regional cancer registry	1975–2005	1526	2·6	1·0–5·7	NA
Johannsson 1999[30]	Southern Sweden	Cohort: pedigree analysis of large *BRCA1/2* families in which index cases were confirmed to have *BRCA1/2* mutations by genetic testing. Risk was assessed for the family as a whole, including mutation carriers and nonmutation carriers, though family branches that were proved or suspected of being noncarriers were excluded Control: compared with incidence in the general population	ICD-7 codes from the population-based Census Registry and the Swedish Cancer Registries	1958–1995	728	2·71	0·56–7·92	0·10

Table 4

Studies of BRCA1/2 mutations in patients with cutaneous melanoma

Study	Patient demographic	Study design	Sample size	Mutations evaluated	Number of mutations
Debniak 2008[51]	Poland	Screened unselected cutaneous melanoma patients and compared with healthy controls	627: melanoma patients 3819–3868: controls	*BRCA2* (T1915M, N991D, N372H), *CHEK2*	*BRCA2* mutations T1915M: 29 (4·6%, OR = 0·8, 95% CI 0·5–1·1, *P* = 0·2) N991D: 59 (9·4%, OR = 1·8, 95% CI 1·3–2·4, *P* = 0·002) N372H: 280 (44·7%, OR = 1·1, 95% CI 0·97–1·4, *P* = 0·1) All mutations: 325 (51·8%, OR = 1·1, 95% CI 0·9–1·2, *P* = 0·6)
Casula 2007[52]	Italy	Screened unselected melanoma patients	557	*BRCA2, CDKN2A, BRAF*	*BRCA2*: 2 (0·4%) *CDKN2A*: 14 (2·5%) *BRAF*: 1 (0·2%)
Monnerat 2007[53]	France	Screened patients with a history of breast cancer and melanoma irrespective of family history. Four patients had a family history of melanoma (at least two cases in a first- or second-degree relative). Nine patients had a family history of breast or/and ovarian cancer. Pathological records of the affected relatives were obtained when possible	82	CDKN2A, CDK4, *BRCA1, BRCA2, TP53*	Deleterious mutations *BRCA1*: 2 patients; one patient had an Ashkenazi founder mutation *BRCA2*: 1 patient *TP53*: 2 patients *CDKNA2*: 2 patients Unclassified mutations *BRCA2*: 5 patients *BRCA1*: 1 patients
Kadouri 2009[38]	Israel	Screened 92 patients of Ashkenazi origin diagnosed with melanoma for three Ashkenazi founder mutations. None of these patients had a relative with melanoma	92	Ashkenazi Jewish Founder *BRCA1/2* mutations	None detected
Landi 2004[57]	Italy	Screened 55 families with at least two relatives with melanoma for various genetic mutations. In three families that had more than one case of breast cancer, *BRCA2* was sequenced. Cancers other than melanoma were not histologically confirmed	3 families (exact number of patients not available)	*BRCA2*	None detected

OR, odds ratio; CI, confidence interval.