The association between cutaneous malignancy and the development of subsequent cancers is well established. Patients with a history of non-melanoma skin cancer (NMSC) are recognized generally to be at increased risk of developing subsequent NMSCs or other cancers. Similarly, individuals diagnosed with melanoma are at increased risk for developing subsequent melanomas and other cancers. Given these known risks, clinical vigilance is indicated for any patient diagnosed with melanoma or NMSC. The manner and degree of patient monitoring depends on the specific presentation, as well as the individual’s personal and family history of disease and the managing physicians’ expertise. Presenting a possible management dilemma for dermatologists is a recognized but poorly understood and possibly underappreciated association between breast cancer in women and malignant melanoma, which is likely based on genetic and hormonal factors. After years of speculation, the accumulating evidence suggests that there is indeed a correlation between cutaneous melanoma and breast cancer and that the relationship may be bi-directional. This finding may have clinical implications for the dermatologist managing a woman with a diagnosis of melanoma or one with a history of breast cancer.

Historical Associations
One of the earliest available publications linking breast cancer and melanoma appeared in the mid-1970s. It documented a series of five cases in which melanoma and breast cancer were diagnosed in the same patient. In four of the five cases, melanoma developed after breast carcinoma. A later analysis of a Connecticut cancer registry found that the rate of diagnosis in the same patient of both breast cancer and melanoma of the skin or eye was more than 60 percent higher than the rate that would be predicted for sporadic disease in the general population. A total of 18,010 women primarily diagnosed with

Key Points
Patients with a history of skin cancer are recognized generally to be at increased risk of developing subsequent skin cancers or other cancers. There is a recognized but poorly understood and possibly underappreciated association between breast cancer in women and malignant melanoma. Studies have suggested an increased risk for breast cancer in patients diagnosed with melanoma and vice versa, though a lack of consensus regarding the degree and nature of the association persists. Some studies have failed to show any clear association between the two. A number of potential hormonal and/or genetic factors are being explored as possibly contributing to the association between breast cancer and malignant melanoma.

For all melanoma patients, clinicians should obtain a thorough history of any cancer. All dermatology patients with a history of breast cancer should receive thorough skin exams and be encouraged to undertake regular and careful skin self-examinations. These individuals should present to the office for skin exams annually or more frequently. All female melanoma patients, especially those with a personal or family history of breast cancer, may be referred to a breast clinic for evaluation. Such patients should be encouraged, at a minimum, to comply with the American Cancer Society’s recommendation for annual mammography and undergo routine breast examinations, provided at regular intervals by a trained physician as well as at home by the patient.
breast cancer and 835 women primarily diagnosed with cutaneous or ocular melanoma were followed up in the Connecticut Tumor Registry. Of these, 23 had both types of tumors diagnosed at least one month apart, compared to the 14 or fewer predicted.

An increase in melanomas among patients initially diagnosed with breast carcinoma was also reported in a Danish cohort. This analysis involved a large sample of 55,000 women diagnosed with breast cancer in Denmark between 1943 and 1980. Findings suggest that women with breast cancer are at increased risk for developing any subsequent cancer, given a higher than predicted incidence of multiple primary tumors in the group. While cancers of the lung, bone, and connective tissue were common and potentially linked to breast cancer treatments, researchers also found an excess in incidence of malignant melanoma in this population.

Based on an analysis of data for patients in one registry, Levi, et al. calculated a standardized incidence ratio (SIR) of 1.4 for malignant melanoma in women who had been diagnosed with breast cancer. The sample of 9,729 breast cancer patients were registered by the Swiss Cancer Registries of Vaud and Neuchâtel and followed up from 1974 to 1998. The largest excess risk was found for soft tissue sarcomas (STS) with an SIR of 3.2. Other cancers with an SIR similar to melanoma included endometrium (1.5), ovary (1.3), colorectum (1.1), gallbladder (1.4), kidney (1.4), lymphomas (1.4), and leukemias (1.2).

Interestingly, another study suggests that the SIR for developing breast cancer after melanoma is 1.4. Specifically among patients diagnosed with melanoma in situ, researchers found an increased risk for secondary tumors, with a statistically significant increase in risk of 1.4 for breast cancer in women. This analysis of 3,766 Swedish patients with a diagnosis of cutaneous melanoma in situ from 1958 to 1992 found that among women, there was a non-significant increased risk of other cancers, including non-Hodgkin's lymphoma (SIR = 1.9), multiple myeloma (3.2), colon cancer (1.6), and pancreas cancer (1.6).

Goggins, et al. identified a modest but statistically significant increase of cutaneous melanoma among breast cancer survivors and vice versa. They followed female breast cancer patients and female cutaneous melanoma patients registered in the 1973-1999 SEER database for development of second primary tumors. Young breast cancer patients (age ≤50), specifically, had a 46 percent increase in the risk for developing cutaneous melanoma. Women who underwent radiation therapy for breast cancer had a 42 percent increase in risk for cutaneous melanoma relative to those who did not. Overall, the risk of developing breast cancer for a melanoma patient was 11 percent, and the risk of developing cutaneous melanoma in a breast cancer patient was 16 percent.

**Contradictory Data**

Despite the good deal of data suggesting an association between breast cancer and malignant melanoma, a lack of consensus regarding the degree and nature of the association remains. Some studies have failed to show any clear association between the two. In a cohort of 20,354 patients in the Swedish Cancer Register from 1958-1988, patients previously diagnosed with malignant melanoma had increased risk for a second primary melanoma or non-melanoma skin cancer, neuroectodermal cancers, and cancers involving the immune system. Despite elevated risk for endometrial cancers, no increased risk for cancers of the breast, ovary, testis or other endocrine glands was seen in this sample. The same researchers had uncovered an elevated risk for breast cancer in the smaller melanoma in situ population cited above.

Another analysis aimed at identifying any effect of breast cancer treatment on risk of developing subsequent primary cancers found no increased risk for malignant melanoma in the cohort. The 16,705 breast cancer patients included in the analysis had been treated with chemotherapy (various regimens), radiotherapy (high-energy photons from a 60Co unit or linear accelerator) and/or hormone therapy (two to five years of tamoxifen).

**Recent Findings**

In a 2009 publication, Murphy, et al. offered additional support for an association between breast cancer and malignant melanoma. In light of a series of patients diagnosed either with a primary melanoma and subsequent breast cancer or primary breast cancer and subsequent melanoma over a six month period in their clinic, the researchers undertook a review of data from the National Irish Cancer Registry. This is a national histology-based registry for all cancers diagnosed since 1994.

In the 10-year period from 1994 to 2004, they uncovered a four-fold increase in the number of individuals with both breast cancer and melanoma compared to the predicted rate. The age standardized incidence of breast cancer was 0.7 per 10^5 for men and 75.6 per 10^5 for women. The age standardized incidence of malignant melanoma was 10.6 per 10^5 for men and 16.1 per 10^5 for women. Based on these numbers, approximately 30-35 individuals should have presented with both cancers. The actual number of patients with both cancers was 127.
Exploring Links

A number of potential hormonal and/or genetic factors are being explored as possibly contributing to the association between breast cancer and malignant melanoma. In their analysis, Goggins, et al. specifically considered evidence that carriers of mutations in the breast cancer predisposition gene, BRCA2, have an increased risk of melanoma and that carriers of mutations in the melanoma susceptibility gene CDKN2A exhibit a higher than expected risk of breast cancer. In a Swedish cohort, it was shown that CDKN2A 113insArg mutation families with melanoma had increased rates of breast cancer in females. Six of the 113insArg families had at least one member with multiple primary melanomas and a total of eight breast cancers (versus the expected 2.1; \( P = .0014 \)).

MC1R has been linked to both breast cancer and melanoma. MC1R variants were found to be associated with an increased risk of melanoma in carriers, and were positively associated with melanoma risk in first degree relatives of carriers. However, there was no association of MC1R variants and breast cancer risk in the studied cohort.

XPD gene variants have also been suggested to influence the risk for melanoma and breast cancer. In a genotyping study, results of analyses of linkage disequilibrium and haplotype frequency suggested that a combination of at least two SNPs (Lys751Gln_CC/Gly156Gly_CC or Lys751Gln_CC/Asp312Asn_AA) inherited as a haplotype was associated with disease.

Because matrix metalloproteinases (MMPs) are associated with both malignant melanoma and breast cancer, a very recent study was undertaken to elucidate a possible association of MMP1 and MMP8 gene variation with each type of cancer. While the study showed that the MMP8 gene rs11225395 polymorphism was associated with the risk of developing malignant melanoma (odds ratio: 1.69; 95% confidence interval: 1.02-2.80; \( P = 0.040 \)) for the A/A genotype and 1.49 (95% confidence interval: 1.03-2.17; \( P = 0.035 \)) for the A/G genotype, compared with the G/G genotype, there was no association detected between this variant and breast cancer susceptibility. Furthermore, there was no strong association between MMP1 variation and the risk of malignant melanoma or breast cancer.

### Table 1. Summary of Studies

<table>
<thead>
<tr>
<th>Positive Association</th>
<th>Cohort/Sample</th>
<th>Sample Description</th>
<th>Findings</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>Connecticut Tumor Registry</td>
<td>18,010 women with BC, 835 with cutaneous or ocular melanoma</td>
<td>60 percent higher rate of concomitant BC and MM</td>
</tr>
<tr>
<td></td>
<td>Danish Cohort</td>
<td>55,000 women with BC in Denmark, 1943-1980</td>
<td>Increased risk for developing any subsequent cancer; “excess of MM”</td>
</tr>
<tr>
<td></td>
<td>Swiss Cancer Registries of Vaud and Neuchâtel</td>
<td>9,729 BC patients</td>
<td>SIR for MM=1.4</td>
</tr>
<tr>
<td></td>
<td>Swedish cohort</td>
<td>3,766 Swedish patients with CM in situ, 1958-1992</td>
<td>SIR for BC=1.4</td>
</tr>
<tr>
<td></td>
<td>SEER</td>
<td>Female BC and CM patients, 1973-1999</td>
<td>Overall, risk of BC in a CM patient=11%; risk of CM in a BC patient=16%</td>
</tr>
<tr>
<td></td>
<td>National Irish Cancer Registry</td>
<td>Patients with CM and MM, 1994-2004</td>
<td>Four-fold increase in patients with BC/CM</td>
</tr>
<tr>
<td>No Association</td>
<td>Swedish Cancer Register</td>
<td>20,354 MM patients, 1958-1988</td>
<td>No increased risk for cancers of the breast, ovary, testis or other endocrine glands</td>
</tr>
<tr>
<td></td>
<td>Curie Institute Cohort</td>
<td>16,705 BC survivors</td>
<td>No increased MM risk</td>
</tr>
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</table>
Two melanoma associated antigen gene transcripts (MAGE-A3, MAGE-A4 mRNA) recently were shown to be associated with breast cancer in women. Specifically, the presence of MAGE-A3 was significantly associated with nodal status (P = 0.009), tumor size (P = 0.009), and American Joint Committee on Cancer stage (P = 0.009); MAGE-A4 positivity was significantly associated with histological grade (P = 0.020).

Supporting a potential role for hormones is evidence that hormone replacement therapy is associated with a slight but statistically significant increase in breast cancer risk and a slight increase in melanoma risk. When researchers analyzed the risk for developing skin cancer in a cohort of women who had received hormone replacement therapy, they found an increased incidence of malignant melanoma, though the increase did not reach statistical significance. In this same population, there was a slightly increased, statistically significant risk of breast cancer. Data were not available regarding concomitant cancers. Nonetheless, the role of estrogen in malignant melanoma remains unclear.

Implications for Care

Despite inconsistencies in the data, the accumulated evidence to date suggests that there is, indeed, an association between breast cancer and malignant melanoma. Thus, a woman diagnosed with one is at increased risk of the other. Therefore, patient education and long-term monitoring must address this possible association.

For all melanoma patients, clinicians should obtain a thorough history of any cancer, especially breast carcinoma. All dermatology patients with a history of breast cancer should receive thorough skin exams and be encouraged to undertake regular and careful skin self-examinations. These individuals should present to the office for skin exams annually or more frequently, depending on their risk level.

Female melanoma patients, especially those with a personal or family history of breast cancer, may be referred to a breast clinic for evaluation. Such patients should be encouraged, at a minimum, to comply with the American Cancer Society's recommendation for annual mammography. In addition to mammography, MRI may be appropriate for some. Female melanoma patients should be encouraged to undergo routine breast examinations, provided at regular intervals by a trained physician as well as at home by the patient. Monthly skin and breast self-exams may be encouraged by the dermatologist.