PUBMED ABSTRACTS CONCERNING THE INCIDENCE OF MELANOMA AND BREAST CANCER IN THE SAME PATIENTS.

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August 2011

Summary

1. The hypothesis was tested that there is a link between melanoma and breast cancer. Specifically literature (Pubmed Abstracts) were consulted concerning evidence that patients with cutaneous melanoma have an increased risk for breast cancer and vice versa that patients with breast cancer have a higher risk for melanoma.
2. No convincing evidence could be found linking breast cancer as a second primary malignancy to cutaneous melanoma.
3. However, considerable evidence could be found linking cutaneous melanoma as a second primary malignancy to breast cancer. Thirteen out of nineteen abstracts supported this hypothesis.
4. The average Standardised Incidence Ratio (SIR) of six values reported was 2.22 (Range: 1.07 – 4.6). This means that the incidence of melanomas in women who have/had breast cancer was more than double what which was expected.
5. It is suggested that this link between breast cancer and melanoma may be due to certain oncogenes in breast cancer and melanoma cells being similar – but, as yet, there is no clarity on the molecular basis of this matter.
6. This information suggests that women who have/had breast cancer or who have breast cancer in the family should be particularly careful not to become overexposed to the sun because they may be more susceptible to cutaneous melanoma.

Summary from Pubmed abstracts

		Yes/No	
1	**Primary =melanoma Secondary breast?**	**Yes**	**O/E =1.1***
2	**Primary =melanoma Secondary breast?**	**Yes**	**N.A.****
3	**Primary =melanoma Secondary breast?**	**Yes**	**1.07 (SIR)*****
4	**Primary =melanoma Secondary breast?**	**No**	**N.A.****
5	**Primary = Breast Secondary melanoma?**	**Yes**	**Highly significant**
6	**Primary = Breast Secondary melanoma?**	**Yes**	**1.29 (SIR)**
7	**Primary = Breast Secondary melanoma?**	**Yes**	**1.1 (HR)********
8	**Primary = Breast Secondary melanoma?**	**Yes**	**2.25(SIR)**
9	**Primary = Breast Secondary melanoma?**	**Yes**	**N.A.**
10	**Primary = Breast Secondary melanoma?**	**YES**	**N.A.**
11	**Primary = Breast Secondary melanoma?**	**NO**	
12	**Primary = Breast Secondary melanoma?**	**NO**	
13	**Primary = Breast Secondary melanoma?**	**YES**	**80%**
14	**Primary = Breast Secondary melanoma?** *"The high constant incidence curve of **second** CMM (cutaneous malignant melanoma) is compatible with the occurrence of a single*	**YES**	**4.6(SIR)**

	mutational event in a population of susceptible individuals."		
15	**Primary = Breast Secondary melanoma?**	**YES**	**1.4 (SIR)**
16	**Primary = Breast Secondary melanoma?**	**NO**	
17	**Primary = Breast Secondary melanoma?**	**NO**	
18	**Primary = Breast Secondary melanoma?**	**NO**	
19	**Primary = Breast Secondary melanoma?**	**YES**	**2.7(SIR)**
	Score for breast =primary and melanoma = second primary	**Yes=13 No=6**	**Average SIR=2.22**

Abbreviations:

1. *** O/E (Observed / expected ratio)**
2. **** N.A. (Not available. No data given in abstract)**
3. ***** SIR (Standardised Incidence Ratio, Observed rate/expected rate)**
4. ****** HR Hazard Ratio**

PUBMED ABSTRACTS

1. Arch Dermatol. 2010 Mar;146(3):265-72.

Increased risk of second primary cancers after a diagnosis of melanoma.

Bradford PT, Freedman DM, Goldstein AM, Tucker MA.

Source

Genetic **Epidemiology** Branch, Division of **Cancer Epidemiology** and Genetics, National **Cancer** Institute, National Institutes of Health, 6120 Executive Boulevard, Rockville, MD 20852, USA. bradfordp@mail.nih.gov

Abstract

OBJECTIVE:

To quantify the risk of subsequent primary cancers among patients with primary cutaneous malignant **melanoma**.

DESIGN:

Population-based registry study.

SETTING:

We evaluated data from 9 **cancer** registries of the Surveillance, **Epidemiology**, and End Results program from 1973-2006.

PARTICIPANTS:

We included 89 515 patients who survived at least 2 months after their initial **melanoma** diagnosis.

RESULTS:

Of the patients with **melanoma**, 10 857 (12.1%) developed 1 or more subsequent primary cancers. The overall risk of a subsequent primary **cancer** increased by 28% (observed to expected [O:E] ratio = 1.28). One quarter of the cancers were subsequent primary melanomas

(O:E = 8.61). Women with head and neck **melanoma** and patients younger than 30 had markedly increased risks (O:E = 13.22 and 13.40, respectively) of developing a subsequent **melanoma**. Second melanomas were more likely to be thin than were the first of multiple primary melanomas (thickness at diagnosis <1.00 mm, 77.9% vs 70.3%, respectively; P < .001). **Melanoma** survivors had increased risk of developing several cancers; the most common cancers with elevated risks were **breast**, prostate, and non-Hodgkin lymphoma (O:E = 1.10, 1.15, and 1.25, respectively).

CONCLUSIONS:

Melanoma survivors have an approximately 9-fold increased risk of developing subsequent **melanoma** compared with the general population. The risk remains elevated more than 20 years after the initial **melanoma** diagnosis. This increased risk may be owing to behavioral factors, genetic susceptibility, or medical surveillance. Although the percentage of subsequent primary melanomas thicker than 1 mm is lower than for the first of multiple primary melanomas, it is still substantial. **Melanoma** survivors should remain under surveillance not only for recurrence but also for future primary melanomas and other cancers

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2. **Melanoma** Res. 2010 Jun;20(3):203-11.

Synchronous and metachronous malignancies in patients with melanoma: a clinicopathologic study highlighting the role of fine-needle biopsy cytology and potential diagnostic pitfalls.

Cooper CL, Murali R, Doubrovsky A, Watson GF, McKenzie PR, Thompson JF, Scolyer RA.

Source

Tissue Pathology and Diagnostic Oncology, Royal Prince Alfred Hospital, Sydney Medical School, The University of Sydney, Sydney, New South Wales, Australia.

Abstract

Fine-needle biopsy (FNB) is commonly used in the investigation of patients with a history of **melanoma** who present with possible metastatic disease. Non-**melanoma** malignancies (NMM) are common in the general population and not infrequent in patients with **melanoma**. Such

tumors may be difficult to distinguish from metastatic **melanoma** on FNB. We sought to determine the types of NMMs that occur in **melanoma** patients, to document the frequency with which they were diagnosed by FNB, and to highlight potential pitfalls in cytologic diagnosis. NMMs occurring in 1416 consecutive **melanoma** patients who underwent FNB of 2204 clinically suspicious lesions between 1992 and 2002 at a single center were reviewed and analyzed. The sites of FNB included lymph nodes (36.9%), skin and subcutis (25.1%), visceral locations (17.9%), and other sites (20.0%). Of the 1416 **melanoma** patients investigated by FNB, 116 (8.2%) had a metachronous or synchronous NMM; the NMM was diagnosed by the FNB in 17 (14.7%) patients. The most common NMMs were epithelial tumors (69.4%, most commonly carcinomas of large bowel, **breast** and prostate) and hematologic malignancies (21.8%). As NMMs are not infrequent in patients with **melanoma**, they should always be considered in the differential diagnosis of clinically suspicious masses in patients with a history of **melanoma**, as well as in patients at high risk of **melanoma**. Careful assessment of the FNB cytologic features and directed use of ancillary studies should enable accurate diagnosis in most cases and facilitate appropriate patient management

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3. J Am Acad Dermatol. 2010 May;62(5):757-67. Epub 2010 Mar 12.

Risk of second primary malignancies following cutaneous melanoma diagnosis: a population-based study.

Spanogle JP, Clarke CA, Aroner S, Swetter SM.

Source

Department of Dermatology, Pigmented Lesion and **Melanoma** Program, Stanford University Medical Center, Stanford, CA, USA.

Abstract

BACKGROUND:

Understanding risk patterns for developing a **second primary** malignancy (SPM) after cutaneous **melanoma** (CM) has implications for both research and clinical practice, including **cancer** screening.

OBJECTIVE:

We sought to describe incidence patterns of SPMs occurring after CM.

METHODS:

We calculated incidence rates and relative risks for the development of 65 different SPMs occurring in 16,591 CM survivors during 1.3 million person-years of observation in the Surveillance, Epidemiology, and End Results program data from 1973 to 2003.

RESULTS:

Compared with the general population, CM survivors had a 32% higher risk of developing any SPM and demonstrated significantly elevated risks for 13 cancers: **melanoma** of the skin (standardized incidence ratio [SIR] 8.99), soft tissue (SIR 2.80), **melanoma** of the eye and orbit (SIR 2.64), nonepithelial skin (SIR 2.31), salivary gland (SIR 2.18), bone and joint (SIR 1.70), thyroid (SIR 1.90), kidney (SIR 1.29), chronic lymphocytic leukemia (SIR 1.29), brain and nervous system (SIR 1.31), non-Hodgkin lymphoma (SIR 1.25), prostate (SIR 1.13), and female **breast** (SIR 1.07). Risks of **second primary melanoma** of the skin, **melanoma** of the eye and orbit, and cancers of the prostate, soft tissue, salivary gland, and bone and joint were elevated throughout the study period, implying no surveillance bias.

LIMITATIONS:

Possible underreporting of CM incidence in **cancer** registries is a limitation. In addition, the lack of individual-level data in **cancer** registry data precludes detailed examination of coincident risk factors.

CONCLUSION:

Risks of particular SPMs after CM may be explained by surveillance bias or shared risk factors. However, these probably do not explain the increased risks observed for prostate, soft tissue, salivary gland, and bone and joint cancers years after CM diagnosis. Further investigation into genetic or environmental commonalities between CM and these cancers is warranted.

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4. **Melanoma** Res. 2008 Jun;18(3):230-4.

The risk of developing a second, different, cancer among 14 560 survivors of malignant cutaneous melanoma: a study by AIRTUM (the Italian Network of Cancer Registries).

Crocetti E, Guzzinati S, Paci E, Falcini F, Zanetti R, Vercelli M, Rashid I, De Lisi V, Russo A, Vitarelli S, Ferretti S, Mangone L, Cesaraccio R, Tumino R, Pannozzo F.

Source

Tuscany **Cancer** Registry, Clinical and Descriptive Epidemiology Unit, CSPO, Florence, Italy. e.crocetti@cspo.it

Abstract

The aim of this study was to provide further quantitative data on the risk of **second** nonmelanoma cancers in patients with cutaneous malignant **melanoma** (CMM). A cohort of 14 560 population-based patients from the Italian Network of **Cancer** Registries incident during 1985-2002 were included and followed up for further incident cases and vital status. Standardized incidence ratios (SIR) were used to compare the number of observed **second** cancers with expected cancers. In a total of 69 581 person-years, 1020 **second** cancers were registered, of which 804.6 were expected (SIR=1.27; 95% confidence interval 1.19-1.35). The risk was similar for males and females, (SIR=1.27 and 1.26, respectively). The risk was slightly higher among younger (<60 years; SIR=1.44) than older (60+ years; SIR=1.19) patients. The overall risk in the period after CMM diagnosis did not change significantly (SIR=1.34 during the first 5 years and 1.12 afterwards). No differences in the overall risk were evident in different years of diagnosis, for different **melanoma** morphology types or for different geographical areas within Italy. Statistically significantly increased risks were found for nonmelanoma skin cancers [observed number (n)=362, SIR=3.12], for bone (n=5, SIR=6.08) and for kidney cancers (n=39, SIR=1.95) and lower than expected risks were found for liver (SIR=0.46) and lung cancers (SIR=0.71). We confirm that CMM patients are at high risk for nonmelanoma skin cancers. The reasons for the increased risk of kidney and bone cancers are not yet clear.

No. 5

Eur J Gynaecol Oncol. 2009;30(6):661-3.

Incidence of multiple primary malignancies in women diagnosed with breast cancer.

Stracci F, D'Alò D, Cassetti T, Scheibel M, La Rosa F.

Source

Umbrian Population **Cancer** Registry, Department of Medical-Surgical Specialties and Public Health, Public Health Section, Perugia University, Perugia, Italy.

Abstract

Using data from the Umbrian Population **Cancer** Registry (RTUP) we tested the hypothesis of relationships between several subsequent **cancer** sites in women who had had **breast cancer**. New patients (7,840) were collected from the RTUP between 01/01/1994 and 31/12/2006; 24 DCO cases were excluded; 332 successive multiple cancers in 320 patients were recorded. Including all **second** cancers, metachronous contralateral **breast cancer**, the observed/expected ratio (SIR) was non-significant. Excluding these cases, SIR was significantly lower whether with or without **second** skin carcinomas. SIR of all **second** metachronous contralateral cancers, excluding skin carcinomas, was non-significant. Significantly lower risk involved the colorectum, stomach, pancreas and metachronous **breast** with different histology. A significant excess was found of **melanoma** and total **second breast** cancers, including the contralateral. The excessive skin **melanoma** in **breast cancer** survivors was attributed to the relationship with BRCA2 and CDKN2A mutation-positive patients. The excess risk due to the CDKN2A mutation should also include pancreatic **cancer** which, in the present study, presented a significantly lower risk

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No. 6

nt J **Cancer**. 2006 May 1;118(9):2285-92.

Risk of second cancer among women with breast cancer.

Mellemkjaer L, Friis S, Olsen JH, Scélo G, Hemminki K, Tracey E, Andersen A, Brewster DH, Pukkala E, McBride ML, Kliewer EV, Tonita JM, Kee-Seng C, Pompe-Kirn V, Martos C, Jonasson JG, Boffetta P, Brennan P.

Source

Institute of **Cancer** Epidemiology, Danish **Cancer** Society, Copenhagen, Denmark. lene@**cancer**.dk

Abstract

A large number of women survive a diagnosis of **breast cancer**. Knowledge of their risk of developing a new **primary cancer** is important not only in relation to potential side effects of their **cancer** treatment, but also in relation to the possibility of shared etiology with other types of **cancer**. A cohort of 525,527 women with **primary breast cancer** was identified from 13 population-based **cancer** registries in Europe, Canada, Australia and Singapore, and followed for **second primary** cancers within the period 1943-2000. We used **cancer** incidence rates of first **primary cancer** for the calculation of standardized incidence ratios (SIRs) of **second primary**

cancer. Risk of **second primary breast cancer** after various types of nonbreast **cancer** was also computed. For all **second cancer** sites combined, except contralateral **breast cancer**, we found a SIR of 1.25 (95% CI = 1.24-1.26) on the basis of 31,399 observed cases after first **primary breast cancer**. The overall risk increased with increasing time since **breast cancer** diagnosis and decreased by increasing age at **breast cancer** diagnosis. There were significant excesses of many different **cancer** sites; among these the excess was larger than 150 cases for stomach (SIR = 1.35), colorectal (SIR = 1.22), lung (SIR = 1.24), soft tissue sarcoma (SIR = 2.25), **melanoma** (SIR = 1.29), non-**melanoma** skin (SIR = 1.58), endometrium (SIR = 1.52), ovary (SIR = 1.48), kidney (SIR = 1.27), thyroid gland (SIR = 1.62) and leukaemia (SIR = 1.52). The excess of **cancer** after a **breast cancer** diagnosis is likely to be explained by treatment for **breast cancer** and by shared genetic or environmental risk factors, although the general excess of **cancer** suggests that there may be additional explanations such as increased surveillance and general **cancer** susceptibility

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No.7

J Clin Oncol. 2008 Mar 10;26(8):1239-46.

Risk of new primary nonbreast cancers after breast cancer treatment: a Dutch population-based study.

Schaapveld M, Visser O, Louwman MJ, de Vries EG, Willemse PH, Otter R, van der Graaf WT, Coebergh JW, van Leeuwen FE.

Source

Comprehensive **Cancer** Center North-Netherlands (CCCN), P.O. Box 330, 9700 AH Groningen, The Netherlands. m.schaapveld@ikn.nl

Abstract

PURPOSE:

To assess the risk of secondary nonbreast cancers (SNBCs) in a recently treated population-based cohort of **breast cancer** patients focused on the association with treatment and prognostic implications.

PATIENTS AND METHODS:

In 58,068 Dutch patients diagnosed with invasive **breast cancer** between 1989 and 2003, SNBC risk was quantified using standardized incidence ratios (SIRs), cumulative incidence, and Cox regression analysis, adjusted for competing risks.

RESULTS:

After a median follow-up of 5.4 years, 2,578 SNBCs had occurred. Compared with the Dutch female population at large, in this cohort, the SIR of SNBCs was increased (SIR, 1.22; 95% CI, 1.17 to 1.27). The absolute excess risk was 13.6 (95% CI, 9.7 to 17.6) per 10,000 person-years. SIRs were elevated for cancers of the esophagus, stomach, colon, rectum, lung, uterus, ovary, kidney, and bladder cancers, and for soft tissue sarcomas (STS), **melanoma**, non-Hodgkin's lymphoma, and acute myeloid leukemia (AML). The 10-year cumulative incidence of SNBCs was 5.4% (95% CI, 5.1% to 5.7%). Among patients younger than 50 years, radiotherapy was associated with an increased lung **cancer** risk (hazard ratio [HR] = 2.31; 95% CI, 1.15 to 4.60) and chemotherapy with decreased risk for all SNBCs (HR = 0.78; 95% CI, 0.63 to 0.98) and for colon and lung **cancer**. Among patients age 50 years and older, radiotherapy was associated with raised STS risk (HR = 3.43; 95% CI, 1.46 to 8.04); chemotherapy with increased risks of **melanoma**, uterine **cancer**, and AML; and hormonal therapy with all SNBCs combined (HR = 1.10; 95% CI, 1.01 to 1.21) and uterine **cancer** (HR = 1.78; 95% CI, 1.40 to 2.27). An SNBC worsened survival (HR = 3.98; 95%CI 3.77 to 4.20).

CONCLUSION:

Breast cancer patients diagnosed in the 1990 s experienced a small but significant excess risk of developing an SNBC

No.8

Int J Gynecol Cancer. 2009 Nov;19(8):1358-63.

Distribution of second primary malignancies suggests a bidirectional effect between breast and endometrial cancer: a population-based study.

Cortesi L, De Matteis E, Rashid I, Cirilli C, Proietto M, Rivasi F, Federico M.

Source

Dipartimento di Oncologia ed Ematologia, Università di Modena e Reggio Emilia, Modena, Italy. hbc@unimo.it

Abstract

INTRODUCTION:

The aim of this study was to investigate the incidence of **second primary** tumors in patients with **breast** cancer (BC), with particular regard to bidirectional risk for endometrial cancer (EC).

METHODS:

A total of 7512 and 343 patients with first and **second primary** BC, respectively, were referenced to the expected number of cases calculated using the standardized incidence ratio (SIR) over the same period, to evaluate the observed and expected ratio between the groups. Data on tamoxifen use were also considered.

RESULTS:

A total of 499 women with **primary** BC developed a **second** tumor. The total SIR, that is, the ratio between observed **second primary** cancer among patients with BC and the expected **primary** cancers in the general population, was significantly higher (SIR = 1.23; 95% confidence interval, 1.12-1.34; P = 0.007), particularly for **melanoma** (2.25), EC (2.15), ovarian cancer (1.74), hematologic malignancies (1.36), and bilateral BC (1.25). A greater risk of BC after thyroid (2.22) and EC (1.62) was also observed. Furthermore, the risk of developing EC was higher in patients treated with tamoxifen (SIR = 2.50 vs 1.34).

CONCLUSIONS:

Bidirectional risk of endometrial cancer was not exclusively related to tamoxifen use

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No.9

Melanoma Res. 2009 Aug;19(4):211-4.

Germline mutations in CDKN2A are infrequent in female patients with melanoma and breast cancer.

Nagore E, Montoro A, García-Casado Z, Botella-Estrada R, Insa A, Lluch A, López-Guerrero JA, Guillén C.

Source

Department of Dermatology, Instituto Valenciano de Oncologia, C/ Profesor Beltran Baguena, 8, Valencia 46009, Spain. eduyame@meditex.es

Abstract

Carriers of mutations in the **melanoma** susceptibility gene, CDKN2A, exhibit a higher than expected risk of **breast** cancer. In this study, we aimed to determine mutations in the CDKN2A gene in patients with **melanoma** and additional **breast** cancer. Thirty-one women with histologically confirmed **melanoma** and **breast** cancer were studied for CDKN2A/ARF gene mutations by direct sequencing analysis. We identified four CDKN2A germline mutations. Two patients harbored the A148T polymorphism, one of them with family history of **breast** cancer. Another patient, with a **melanoma** diagnosed at 77 years, a **breast** cancer diagnosed at 66 and a family history of **melanoma**, had the V59G mutation. The fourth patient had a **melanoma** diagnosed at 54 years, a **breast** cancer at 46, and a strong family history of **breast** cancer (mother and grandmother), and presented the A85T mutation. The epidemiologic link between cutaneous **melanoma** and **breast** cancer is not mainly related to CDKN2A mutations. However, some mutations might have a role in this association or even in familial **breast** cancer, as it could be inferred from the patient with the A85T mutation

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No.10

Fam Cancer. 2007;6(4):453-61. Epub 2007 Jul 12.

BRCA1, BRCA2, TP53, and CDKN2A germline mutations in patients with breast cancer and cutaneous melanoma.

Monnerat C, Chompret A, Kannengiesser C, Avril MF, Janin N, Spatz A, Guinebretière JM, Marian C, Barrois M, Boitier F, Lenoir GM, Bressac-de Paillerets B.

Source

Department of Genetics, Institut Gustave Roussy, 39 rue Camille Desmoulins, Villejuif Cedex, France.

Abstract

PURPOSE:

From epidemiological studies it appears that **breast** cancer (BC) and cutaneous **melanoma** (CMM) in the same individual occur at a higher frequency than expected by chance. Genetic

factors common to both cancers can be suspected. Our goal was to estimate the involvement of "high risk" genes in patients presenting these two neoplasia, selected irrespectively from family history and age at diagnosis.

EXPERIMENTAL DESIGN:

Eighty two patients with BC and CMM were screened for BRCA1, BRCA2, TP53, CDKN2A and CDK4 (exon 2) germline mutations.

RESULTS:

Deleterious mutations were identified in 6 patients: two carriers of a BRCA1 germline mutation, two carriers of TP53 germline mutations (one of which also harbored a BRCA2 deleterious mutation, the other one a BRCA2 unclassified variant), and two carriers of a CDKN2A germline mutation. In addition, 6 variants of unknown signification were identified in BRCA1 or BRCA2 genes. Regarding family history, 3/13 (23%) patients with a positive family history of BC or CMM were carriers of a germline mutation, whereas only 3/69 (4%) patients without family history were carriers of a germline mutation.

CONCLUSION:

Our findings show that few patients with BC and CMM who lacked family histories of these cancers are carriers of deleterious germline mutations in four of the five genes we examined. We describe for the first time, two simultaneous BRCA2 and TP53 mutations, suggesting that analysis in more than one gene could be performed if a patient's personal or familial history does not match a single syndrome

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No.11

Br J Cancer. 2008 Mar 11;98(5):870-4. Epub 2008 Feb 12.

Second malignancies after breast cancer: the impact of different treatment modalities.

Kirova YM, De Rycke Y, Gambotti L, Pierga JY, Asselain B, Fourquet A; Institut Curie **Breast** Cancer Study Group.

Source

Department of Radiation Oncology, Institut Curie, Paris, France. youlia.kirova@curie.net

Abstract

Treatment for non-metastatic **breast** cancer (BC) may be the cause of **second** malignancies in long-term survivors. Our aim was to investigate whether survivors present a higher risk of **malignancy** than the general population according to treatment received. We analysed data for 16 705 BC survivors treated at the Curie Institute (1981-1997) by either chemotherapy (various regimens), radiotherapy (high-energy photons from a 60Co unit or linear accelerator) and/or hormone therapy (2-5 years of tamoxifen). We calculated age-standardized incidence ratios (SIRs) for each **malignancy**, using data for the general French population from five regional registries. At a median follow-up 10.5 years, 709 patients had developed a **second malignancy**. The greatest increases in risk were for leukaemia (SIR: 2.07 (1.52-2.75)), ovarian cancer (SIR: 1.6 (1.27-2.04)) and gynaecological (cervical/endometrial) cancer (SIR: 1.6 (1.34-1.89); P<0.0001). The SIR for gastrointestinal cancer, the most common **malignancy**, was 0.82 (0.70-0.95; P<0.007). The increase in leukaemia was most strongly related to chemotherapy and that in gynaecological cancers to hormone therapy. Radiotherapy alone also had a significant, although lesser, effect on leukaemia and gynaecological cancer incidence. The increased risk of sarcomas and lung cancer was attributed to radiotherapy. No increased risk was observed for malignant **melanoma**, lymphoma, genitourinary, thyroid or head and neck cancer. There is a significantly increased risk of several kinds of **second malignancy** in women treated for BC, compared with the general population. This increase may be related to adjuvant treatment in some cases. However, the absolute risk is small.

No.12

Int J Radiat Oncol Biol Phys. 2007 Jun 1;68(2):359-63. Epub 2007 Mar 26.

Risk of second malignancies after adjuvant radiotherapy for breast cancer: a large-scale, single-institution review.

Kirova YM, Gambotti L, De Rycke Y, Vilcoq JR, Asselain B, Fourquet A.

Source

Department of Radiation Oncology, Institut Curie, Paris, France. youlia.kirova@curie.net

Abstract

PURPOSE:

The aim of this study was to estimate the risk of **second** malignancies (SM) after radiation therapy (RT) for **breast** cancer (BC) in a large, institutional, homogeneous cohort of patients.

METHODS AND MATERIALS:

We retrospectively studied 16,705 patients with nonmetastatic BC treated at the Institut Curie in Paris between 1981 and 1997. Adjuvant RT was given to 13,472 of these patients, and no RT was given to 3,233. The SM included all first nonBCs occurring during follow-up. Cumulative risks for each group were calculated using Kaplan-Meier estimates, censoring for contralateral cancer or death.

RESULTS:

Median patient age at diagnosis of BC was 55 years for the whole population, and 53 and 60 years for patients who had and had not undergone irradiation, respectively. At the 10.5-year median follow-up, 709 patients were diagnosed with SM (113 in the non-RT and 596 in the RT group). There was a significant increase in the rate of sarcomas and lung cancers in the RT group compared with non-RT group (p 0.02). Treatment with RT was not found to increase the risk of other types of cancers such as thyroid cancer, malignant **melanoma**, gastrointestinal or genitourinary, and hematologic SM.

CONCLUSIONS:

This study suggests that adjuvant RT increased the rate of sarcomas and lung cancers, whereas it did not increase the rate of other malignancies

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No.13

Cancer Causes Control. 2006 May;17(4):411-20.

Incidences and trends of second cancers in female breast cancer patients: a fixed inception cohort-based analysis (United States).

Yu GP, Schantz SP, Neugut AI, Zhang ZF.

Source

Biostatistics and Epidemiology Service, The New York Eye and Ear Infirmary, 310 East 14th street, New York, NY 10003, USA. gyu@nyee.edu

Abstract

OBJECTIVE:

To determine incidences and time trends of **second** cancers among female **breast cancer** patients.

METHODS:

Using data of the National **Cancer** Institute's Surveillance, Epidemiology, and End Results (SEER) Program, we designed three inception cohorts: 1975-1977 (n=25,920), 1983-1985 (n=32,722) and 1991-1993 (n=40,819), and analyzed their incidences of **second** cancers during the first 8 years after initial **breast cancer** diagnosis.

RESULTS:

Between the 1970s and the 1990s, the incidence rate of **malignant second cancer** significantly increased among female **breast cancer** patients, of which **second** non-Hodgkin's lymphoma and kidney **cancer** increased by about 150%, while **second** cancers of the thyroid, uterine corpus and skin **melanoma** increased 80%, and **cancer** of the lung increased 50%. The patterns of trend of **second** cancers were somewhat similar to those of the general population except for **second** endometrial **cancer** at all ages and **second** leukemia and skin **melanoma** among young patients aged 20-49. In the 1990s, the risk ratios (RR) of all sites **cancer** were found to be 5.5 (95% CI=5.0-6.1) for age 20-49, 1.3 (1.3-1.4) for age 50-64, and 1.2 (1.1-1.2) for age 65 and over, comparing **breast cancer** patients to general population. Additionally, radiotherapy slightly increased the risks of **second** leukemia (RR=1.8, 1.2-2.8), and **second** endometrial (RR=1.3, 1.0-1.6) and **breast** (RR=1.2, 1.1-1.3) cancers.

CONCLUSIONS:

The fixed inception cohort method is valid for analyzing **cancer** registry-based **second cancer** data. By this method, we found that the incidence of **second cancer** has substantially increased among female **breast cancer** patients over the past 25 years. Observed changes in incidence may partially reflect the effect of treatments. Because the absolute number of affected patients is small, however, the **breast cancer** treatments have remained safe for most patients

No.14

Int J **Cancer**. 2005 Dec 10;117(5):877-9.

High constant incidence rates of second cutaneous melanomas.

Levi F, Randimbison L, Te VC, La Vecchia C.

Source

Cancer Epidemiology Unit and **Cancer** Registry of Vaud, Institut Universitaire de Médecine Sociale et Préventive, Lausanne, Switzerland. fabio.levi@chuv.ch

Abstract

The incidence of most epithelial cancers rises with a power of age. However, **second breast** cancers have a high constant incidence independent of age. The skin is one of the few other sites allowing examination of age incidence curves of **second neoplasms** of the same organ. We considered the risk of **second primary** cutaneous **malignant melanoma** (CMM) in a population-based series of 3,439 first CMM registered and followed-up between 1974 and 2003 in the Swiss Cantons of Vaud and Neuchâtel (about 786,000 inhabitants). A total of 43 cases of **second** CMM were observed vs. 9.3 expected, corresponding to a standardized incidence ratio (SIR) of 4.6. The SIR was 8.5 under age 50, 5.7 at age 50-59 and 3.5 at age 60 or over. At 20 years, the cumulative risk of **second** CMM was 5%. Age-specific incidence rates of **second primary** CMM did not vary across age groups 30-39 through 80+, ranging between 1 and 2.5 per 1,000 person-years. Thus, the risk of CMM is substantially increased in subjects diagnosed with a CMM, and the relative risk is greater at younger age and declines with advancing age. The high constant incidence curve of **second** CMM is compatible with the occurrence of a single mutational event in a population of susceptible individuals

No.15

Ann Oncol. 2003 Jan;14(1):71-3.

Cancer risk in women with previous breast cancer.

Levi F, Te VC, Randimbison L, La Vecchia C.

Source

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Abstract

BACKGROUND:

Excess risks of several **second neoplasms** following **breast cancer** have been reported. However, these risks have still to be quantified.

PATIENTS AND METHODS:

We considered 9,729 **breast cancer** patients registered by the Swiss **Cancer** Registries of Vaud and Neuchâtel (covering about 786,000 inhabitants) and followed up from 1974 to 1998.

RESULTS:

Overall, 443 **second primary neoplasms** (other than **second primary breast** cancers) were observed versus 389 expected [standardised incidence ratio (SIR): 1.14; 95% confidence interval (CI) 1.04-1.25]. The SIRs were above unity for endometrium (SIR = 1.5), ovary (1.3), colorectum (1.1), gallbladder (1.4), cutaneous **malignant melanoma** (1.4), kidney (1.4), lymphomas (1.4) and leukaemias (1.2), as well as for selected tobacco-related **neoplasms**. The largest excess risk was found for soft tissue sarcomas (STS) with 10 cases observed versus 3.1 expected (SIR = 3.2; 95% CI 1.5-5.9). Of these, eight occurred in potentially irradiated areas.

CONCLUSIONS:

This analysis confirms the existence of a modest excess in several **neoplasms** occurring after **breast cancer**. The substantial excess of STS confirms the strong association between irradiation and STS.

No. 16

Cancer. 1984 Jul 1;54(1):145-50.

Multiple primary malignant neoplasms in breast cancer patients in Israel.

Schenker JG, Levinsky R, Ohel G.

Abstract

The data of an epidemiologic study of multiple **primary malignant neoplasms** in **breast cancer** patients in Israel are presented. During the 18-year period of the study 12,302 cases of **breast** carcinoma were diagnosed, and, of these, 984 patients (8%) had multiple **primary malignant** tumors. Forty-seven of these patients developed two multiple **primary** cancers. A significantly higher than expected incidence of **second primary** cancers occurred at the following five sites: the opposite **breast**, salivary glands, uterine corpus, ovary, and thyroid. Cancers of the stomach and gallbladder were fewer than expected. Treatment of the **breast cancer** by irradiation was associated with an increased risk of subsequent cancers of lung and hematopoietic system. The prognosis was mainly influenced by the site and **malignancy** of the **second primary cancer**. The incidence of multiple **primary** malignancies justifies a high level of alertness to this possibility in the follow-up of **breast cancer** patients

No. 17

Second Primary Cancers Following Female Breast Cancer in Osaka, Japan—A Population-Based Cohort Study

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- Received April 8, 1987.
- Accepted August 17, 1987.

Abstract

Using the data accumulated in the Osaka Cancer Registry, a cohort study was conducted on the occurrence of second primary cancers following the first breast cancer in females. Of the 9, 503 breast cancer patients newly diagnosed in the period 1965–1982 who were followed up until the end of 1983 (average follow-up period, 5.7 years), 344 developed second cancers, whereas the expected number had been 211 (relative risk (RR) = 1.6; 95% confidence interval (CI) = 1.5–1.8). The increased risk was observed throughout the observation period, and was higher in patients of less than 45 years of age at diagnosis than in older women. Significant excess risks were found for second cancers of the opposite breast (RR = 4.2; 95% CI = 3.4–5.2), buccal cavity (RR = 3.6; 95% CI = 1.6–7.2), stomach (RR = 1.4; 95% CI = 1.2–1.8), colon (RR = 1.8; 95% CI = 1.1–2.1) and thyroid gland (RR = 3.2; 95% CI % 1.5–6.1). The effects of chemo- and radiotherapy administered for initial breast cancer on the increased risk of the above mentioned second cancers were also examined. These therapeutic measures were found not likely to be related to the excess risks for cancers of the buccal cavity, stomach and colon. For second cancer of the opposite breast, however, both chemotherapy and radiotherapy remained as possible risk factors. The effect of radiation was proposed as being a likely explanation for the excess risk of second thyroid cancer.

No.18

nt J Radiat Oncol Biol Phys. 2002 Feb 1;52(2):406-14.

Second nonbreast malignancies after conservative surgery and radiation therapy for early-stage breast cancer.

Galper S, Gelman R, Recht A, Silver B, Kohli A, Wong JS, Van Buren T, Baldini EH, Harris JR.

Source

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Abstract

PURPOSE:

Breast cancer patients treated with conservative surgery and radiation therapy are at risk of developing **second** nonbreast malignancies (SNBMs). The purpose of this study was to determine the incidence of all SNBMs and SNBMs by specific location among long-term survivors and to compare the risk of these events to the age-specific incidence of malignancies as first cancers in the Surveillance Epidemiology and End-Results Program (SEER) population.

METHODS AND MATERIALS:

We analyzed the likelihood of SNBM development for 1884 patients with clinical Stage I or II **breast cancer** treated with gross excision and > or = 60 Gy (median 63) to the **breast** between 1970 and 1987. Fifty-seven percent received supraclavicular/axillary radiation (median dose 45 Gy, range 20-60) and 28% received systemic therapy. The median age at diagnosis was 52 years. The median clinical tumor size was 2 cm. Patients were considered at risk of an SNBM until the development of the first of distant metastases or contralateral **breast cancer** or death or, if alive and disease-free, until the last follow-up visit. The expected numbers of cancers were obtained from the SEER database, using the age-specific incidence for white women within 5-year age groups and 5-year calendar intervals. The median time at risk for an SNBM was 10.9 years (range 0.2-27.9).

RESULTS:

By 8 years of follow-up, 432 patients (23%) had developed distant metastases, 295 patients (16%) a local/regional recurrence, and 159 (8%) a contralateral **primary**. Of the 1884 patients in

our cohort, 147 (8%) developed an SNBM compared with the 127.7 expected from SEER. This corresponds to an absolute excess of 1% of the study population and a relative increase of 15% greater than that expected from SEER (p = 0.05). Within the first 5 years, the observed and expected rates of SNBMs were identical (47 vs. 46.9). After 5 years, 24% more SNBMs were observed than expected (100 vs. 80.8, p = 0.02). Among patients <50 years old at **breast cancer** diagnosis, 43% more observed SNBMs occurred than expected (40 vs. 28, p = 0.02). For patients > or = 50 years, 7% more SNBMs were observed than expected (107 vs. 99.7, p = 0.25). Lung SNBMs were observed in 33 women, 52% more than the 21.67 predicted by SEER (p = 0.01). Most of the lung SNBMs occurred >5 years after treatment (n = 23) and in women who were >50 years at the time of their **breast cancer** diagnosis (n = 27). The observed incidence of ovarian **cancer** was significantly greater than expected among patients <50 years (7 vs. 1.96, p = 0.004) but was not different than expected for patients > or = 50 years (5 vs. 5.3, p = 0.61). Among the 7 sarcomas, 3 developed in the radiation field.

CONCLUSIONS:

SNBMs occur in a substantial minority (8%) of patients treated with conservative surgery and radiotherapy. However, the absolute excess risk compared with the general population is very small (1%). This excess risk is only evident after 5 years. In particular, a slightly increased incidence of lung SNBMs and a somewhat larger increase in ovarian **cancer** among younger patients was found. Our data suggest that preventive strategies to reduce the incidence of certain cancers (e.g., smoking cessation and prophylactic oophorectomy) and/or continued monitoring for SNBMs to increase the likelihood of early detection and treatment may be prudent in this population

No. 19

Breast Cancer Res Treat. 2000 Jun;61(3):183-95.

Increased risk of second cancers following breast cancer: role of the initial treatment.

Rubino C, de Vathaire F, Diallo I, Shamsaldin A, Lê MG.

Source

Unité de Recherche en Epidemiologie des Cancers de l'Institut National de la Santé et de la Recherche Médicale (U521), Institut Gustave Roussy, Villejuif, France.

Abstract

OBJECTIVES AND METHODS:

The risk of **second primary** malignancies (SMN) was studied in a cohort of 4,416 one-year survivors of a **breast cancer**. The role of the menopausal status and of the initial treatment modalities (surgery, radiotherapy, and chemotherapy) was investigated.

RESULTS:

Excluding **second primary breast cancer** and non-**melanoma** skin **cancer**, a total of 193 (4.4%) patients developed a SMN between 1973 and 1992, compared with 136 expected (Standardised Incidence Ratio, SIR = 1.4, 95% CI (1.2-1.6)). No trend towards either an increase or a decrease was noted in the SIR with time after treatment (p = 0.2). The greatest increase in the relative risk concerned soft tissue cancers (SIR = 13.0, 95% CI: 6.8-22.3), followed by leukaemia (SIR = 3.1, 95% CI: 1.7-5.0), **melanoma** (SIR = 2.7, 95% CI: 1.4-4.8), kidney (SIR = 2.5, 95% CI: 1.2-4.5), ovary (SIR = 2.0, 95% CI: 1.2-3.1) and uterine tumours (SIR = 1.9, 95% CI: 1.4-2.5). The SIR was 3.0 (95% CI 1.8-4.7) in women under 40 at the time of the **breast cancer**, 1.9 (95% CI: 1.4-2.4) in those aged 40-49 and 1.2 (95% CI 1.0-1.4) in those aged 50 or more. In the 2,514 women who had received radiotherapy as initial treatment without chemotherapy, the SIR for all SMN was 1.6 (95% CI: 1.1-2.3) fold higher than in those who had not received radiotherapy as initial treatment.

CONCLUSION:

In conclusion, this study confirms the increased risk of **second** malignancies in women treated for a **breast cancer**, and particularly in those who were younger at the time of treatment for **breast cancer**. Our results also suggest that radiotherapy may play a role in the onset of these **second** lesions