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Second Primary Neoplasms Following Breast Cancer in Saarland, Germany, 1968–1987

Hermann Brenner, Sabine Siegle, Christa Stegmaier and Hartwig Ziegler

A statewide cohort study on the occurrence of second primary neoplasms was conducted among 9678 women first diagnosed with breast cancer in Saarland, Germany between 1968 and 1987. A total number of 409 second primary neoplasms was observed compared to 328 cases that would have been expected based on the incidence rates of the general population (standardised incidence ratio, SIR = 1.25). This elevation in incidence of second neoplasms was primarily due to increased occurrence of cancer of the opposite breast (SIR = 2.48), which was most pronounced for patients below the age of 50 (SIR = 4.20) and within the first 5 years after diagnosis (SIR = 2.91). There was a moderate elevation in incidence of malignant tumours of the ovaries (SIR = 1.46), while the incidence of most other malignancies was lower than in the general population. Our results, which are in agreement with previous findings from Northern Europe, the U.S.A. and Japan provide valuable background information for aetiological research, as well as for surveillance of breast cancer patients.
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INTRODUCTION

STUDIES ON the occurrence of second primary neoplasms in cancer patients serve several purposes: first, these studies may suggest common (or opposite) risk factors of the first and second neoplasms [1]. Second, they may help to monitor potential adverse effects of treatment of the first malignancy, such as radiotherapy or chemotherapy [1–3]. Finally, such studies may provide guidelines for rational long-term surveillance of surviving cancer patients [1].

Overall, the occurrence of second malignancies is a rare event. As a result, the numbers of patients of single hospitals or medical centres usually provide insufficient power for epidemiological studies. Hence, the most important investigations on this topic have been contributed by population-based cancer registries, which have been set up to monitor cancer incidence and prognosis in defined large populations. This monitoring function also provides background incidence rates in the general population,

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with which the incidence rates of second neoplasms in patients with a first cancer may be compared. On the basis of monitoring very large populations over several decades, the nationwide cancer registries of Denmark, Finland and Sweden [4–6] and the cancer registry of Connecticut, U.S.A. [4], as well as international collaborative studies of multiple cancer registries (e.g. [7–10]) have contributed the most comprehensive information on the occurrence of second primary neoplasms to date. In this study, we present the first population-based study on second primary neoplasms following breast cancer from central Europe.

MATERIALS AND METHODS

Study population, data collection, variables

Our study is based on the cancer registry of Saarland, Germany. Saarland is a small state (about 1.05 million inhabitants) in southwest Germany. It is the only state within the western part of Germany, in which reliable and sufficiently complete cancer incidence rates have been recorded throughout the past two decades [11, 12]. Notifications of cancer patients to the state registry are made by the physicians who are involved in the diagnosis and treatment of the cancer patients, including clinicians, general practitioners, radiologists and pathologists.

In this paper, we present a cohort study of women notified to the cancer registry with a first diagnosis of breast cancer (ICD-9 position 174) between 1 January 1968 and 31 December 1987. Multiple notifications on the same patient (including notifications of second primary malignancies) were linked by a sophisticated computer-assisted procedure, which is based on various combinations of orthographic and phonetic codes of the name, the address, sex and date of birth of the patients. A complete mortality follow-up was ensured by routine record linkage with official mortality statistics. The follow-up period for this study terminated on 31 December 1987.

For the purpose of this study, all medical informations given in the original notifications to the registry were reviewed by one of the authors (S.S.). Access to more detailed sources of information, such as hospital records, was not possible due to restrictive data protection laws. Utmost care was given to distinguish second primary neoplasms from eventual metastases, taking all relevant medical information, particularly all histopathological information into account. To reduce the potential for misclassification of second primary neoplasms and metastases, we excluded the first 12 months after diagnosis of the initial tumour from the analysis, since manifestation of metastases is frequent in this time period. We also excluded tumours of unspecified location and secondary malignancies (ICD-9 195-199) as well as the following sites of potential second tumours, which are the preferred locations of breast cancer metastases [13]: liver (ICD-9 position 155), lung (ICD-9 162), bone (ICD-9 170), brain and nervous system (ICD-9 191–192). Finally, skin tumours (ICD-9 172–173) were excluded, as cancer notifications by dermatologists did not always reach satisfactory levels of completeness [12]. The analyses were performed jointly for all remaining malignant neoplasms (ICD-9 140–208), as well as separately for the most common single diagnoses. In addition, stratifications were made by age of the patients at diagnosis of the initial tumour (categories: < 50 years, ≥ 50 years) and by time after the diagnosis (categories: 13–60 month, 61–120 month, 121–240 month).

Statistical analyses

The observed numbers of cases of second primary malignancies were compared with the numbers that would have been expected, had the sex-, age-, and calendar period-specific incidence rates among the breast cancer patients been identical to the corresponding incidence rates of the "general population". These expected numbers (E) were calculated as

$$E = \sum_{i=1}^{n} \sum_{j=0\text{–}4}^{\geq 85} \sum_{k=68\text{–}72}^{83\text{–}87} T_{ijk} \times I_{jk},$$

where n is the number of breast cancer patients, T_{ijk} is the follow-up time (again excluding the first 12 months after diagnosis of the initial breast cancer) of a patient i ($i = 1, \ldots, n$) in age category j (categories: 0–4, 5–9, ..., 80–84, ≥ 85 years) during the calendar period k (categories: 1968–1972, 1973–1977, 1978–1982, 1983–1987), and I_{jk} is the corresponding incidence rates of the female population of Saarland as provided by the cancer registry. The ratio of the numbers of the observed (O) and expected (E) second primary malignancies is the standardised incidence ratio (SIR): SIR = O/E [14]. SIR equals 1.0 if the incidence of second primary neoplasms among the patients equals the incidence of neoplasms in the general population. An SIR above or below 1.0 reflects higher or lower incidence rates among the patients, respectively. For $0 \leq 30$, exact 95% confidence intervals of the SIR were calculated assuming Poisson distribution of the observed numbers of cases [15], for $0 > 30$, 95% confidence intervals were calculated using Byar's approximation [16].

RESULTS

Overall, 43 642.25 person-years of observation were contributed by 9678 women with a first diagnosis of breast cancer between 1968 and 1987.

Table 1 displays the observed and expected numbers and the SIR of the second primary neoplasms of any site, as well as of the most frequent single diagnoses. A total number of 409 malignancies was observed, whereas 328 cases would have been expected (SIR = 1.25). The elevation of incidence among the breast cancer patients compared to the general population essentially results from the high incidence of tumours of the contralateral breast (SIR = 2.48). The incidence of second malignancies excluding the contralateral breast was even lower among breast cancer patients than among the general population (206 observed versus 246 expected cases, SIR = 0.84). The incidence of malignant tumours of the ovaries was moderately elevated (SIR = 1.46); the 95% confidence interval of the SIR, however, includes 1.0 given the small numbers of cases. On the other hand, fewer cancers were observed than expected at the gallbladder and bile ducts (SIR = 0.28), the cervix uteri (SIR = 0.48) and the kidneys (SIR = 0.48).

Table 2 shows the results by age at diagnosis of the initial tumour. As this subdivision leads to very small numbers of cases for some neoplasms, we present only the results for those tumour sites for which the expected numbers exceeded 2.0 in all of the assessed subgroups. The most striking result is the strong excess incidence of cancer of the contralateral breast (SIR = 4.20) along with a clear excess incidence of malignant tumours of the ovaries (SIR = 2.85) among patients whose initial breast cancer was diagnosed before the age of 50. Overall, 98 second primary malignancies of any site were observed in this subgroup, whereas only 41.9 would have been expected from the incidence rates of the general population (SIR = 2.34). In contrast, the number of observed neoplasms of any site only slightly exceeded the number of expected cases in the breast cancer patients above the age of 50 (SIR = 1.09). There was still an excess incidence of

Table 1. Numbers of observed (O) *and expected* (E) *second primary neoplasms, and standardised incidence ratio* (SIR) *with* 95% *confidence interval* (95% CI) *in breast cancer patients. Saarland, Germany,* 1968–1987

Site of second neoplasm	ICD-9	*O*	*E*	SIR	(95% CI)
Stomach	151	24	30.4	0.79	(0.51–1.17)
Colon	153	34	41.5	0.82	(0.57–1.14)
Rectum	154	29	24.5	1.19	(0.80–1.71)
Gallbladder, bile ducts	156	4	14.4	0.28	(0.08–0.72)
Pancreas	157	10	10.4	0.96	(0.46–1.77)
Contralateral breast	174	203	81.9	2.48	(2.15–2.85)
Cervix uteri	180	8	16.7	0.48	(0.21–0.95)
Corpus uteri	182	24	25.6	0.94	(0.60–1.39)
Ovaries	183	22	15.0	1.46	(0.92–2.21)
Urinary bladder	188	12	9.4	1.28	(0.66–2.24)
Kidneys	189	4	8.3	0.48	(0.13–1.23)
Lymphomas and leukaemias	200–208	14	18.2	0.77	(0.42–1.29)
Any site*	140–208*	409	328.3	1.25	(1.13–1.37)

*Excluding neoplasms (ICD-9) of the liver (155), lung (162), bone (170), skin (172–173), brain and nervous system (191–192), and neoplasms of unspecified location and secondary neoplasms (195–199).

contralateral breast cancer in this subgroup (SIR = 2.05), which was almost compensated for, however, by clearly reduced incidence rates of other tumours, such as cervical cancer (SIR = 0.31).

Additional analyses in which stratification by follow-up time was employed revealed the following pattern: the elevation of incidence of contralateral breast cancer was most pronounced in the first 5 years after diagnosis of the initial breast cancer (13–60 months: SIR = 2.91) and decreased during later follow-up periods (61–120 months: SIR = 2.46, 121–240 months: SIR = 1.42). While the number of second malignancies of any site was higher than the expected number during the first 10 years after diagnosis of the initial cancer (13–60 months: SIR = 1.51, 61–120 months: SIR = 1.21), the opposite was true beyond the 10th year of follow-up (SIR = 0.70).

DISCUSSION

The investigation presented in this paper is, to our knowledge, the first population-based study on second primary neoplasms following breast cancer reported from central Europe to date. The most prominent finding of this study is the strong elevation in incidence of cancer of the contralateral breast, whereas the incidence of most other malignant neoplasms is lower than in the general population. The elevation in incidence of contralateral breast cancer is, on a relative scale, particularly pronounced in patients below the age of 50 and in the first 5 years after the diagnosis of the initial cancer. These results are in good agreement with previous findings from Denmark, North America and Japan [17–21]. The magnitude of the elevation of contralateral breast cancer incidence is the more striking since the expected numbers of cases used for comparison refer to either breast, while the observed numbers are restricted to only one (the contralateral) breast. If the observed numbers were to be compared to the expected numbers of just one breast, the SIR of tumours of the contralateral breast would be twice as high.

The frequent occurrence of bilateral breast cancer is not surprising, given the shared risk factors of cancer in both breasts. On the other hand, it can be shown numerically, that the known

Table 2. Numbers of observed (O) *and expected* (E) *second primary neoplasms, and standardised incidence ratio (SIR) with* 95% *confidence interval (95% CI) in breast cancer patients by age at diagnosis. Saarland, Germany,* 1968–1987

		Age < 50 years				Age ≥ 50 years			
Site of second neoplasm	ICD-9	*O*	*E*	SIR	(95% CI)	*O*	*E*	SIR	(95% CI)
Colon and rectum	153–154	3	5.3	0.57	(0.12–1.66)	60	60.7	0.99	(0.76–1.29)
Contralateral breast	174	69	16.4	4.20	(3.27–5.32)	134	65.4	2.05	(1.72–2.43)
Cervix uteri	180	4	3.8	1.05	(0.29–2.69)	4	12.8	0.31	(0.08–0.79)
Corpus uteri	182	1	3.3	0.30	(0.01–1.67)	23	22.2	1.03	(0.65–1.55)
Ovaries	183	7	2.5	2.85	(1.14–5.87)	15	12.6	1.19	(0.67–1.96)
Lymphomas and leukaemias	200–208*	3	2.1	1.46	(0.30–4.26)	11	16.1	0.68	(0.34–1.22)
Any site*	140–208*	98	41.9	2.34	(1.90–2.85)	311	285.9	1.09	(0.97–1.22)

*Excluding neoplasms (ICD-9) of the liver (155), lung (162), bone (170), skin (172–173), brain and nervous system (191–192), and neoplasms of unspecified location and secondary neoplasms (195–199).

risk factors of breast cancer are by far insufficient to account for as strong an association [1]. The same applies to the potential elevation of incidence of contralateral breast cancer resulting from radiotherapy of the first tumour [22]. The potential radiation effects have, however, so far not fully been explored by cancer registry studies due to the lack of sufficiently detailed information on the specifics of the therapy, such as dosimetry [18, 21]. This limitation also applies to our study, which makes it impossible to distinguish potential treatment effects from effects of other aetiological factors. Any relevant elevation of contralateral breast cancer incidence due to radiotherapy in the first 10 years after diagnosis of the first tumour would be extremely unlikely though [2, 18, 23]. Other factors, such as genetic factors [24, 25], are therefore likely to play a major role.

The association between the occurrence of breast cancer and other gynaecological tumours is of particular interest in the light of common or opposite aetiological factors [21]. The elevation of incidence of ovarian cancer found in our study which was stronger among younger breast cancer patients than among older patients is very similar to corresponding results from England [26], Sweden [6], Denmark [27], Finland [5], Connecticut [17] and Japan [19]. This association may be due to common endocrine factors. However, radiotherapy of the ovaries or oophorectomy, which have both been applied in the treatment of premenopausal patients (and which may influence the rate of second ovarian tumours in opposite directions), as well as potential misclassification of tumour metastases in the ovaries must also be taken into consideration [6, 21]. Like the Danish study [27], our study did not confirm an increase in incidence of endometrial cancer among breast cancer patients which was observed in Connecticut [19], Sweden [6] and Finland [5]. The decreased rate of cervical cancer found in our study appears to be plausible in the light of different risk profiles of various subgroups of the population: while breast cancer is more common in women with higher socioeconomic status [28], an inverse relation has been found between socioeconomic status and risk of cervical cancer [29]. In our study, the incidence of cervical cancer among breast cancer patients was about 50% lower than in the general population. A similar result was reported from Sweden [6], but the reduction was less pronounced in most other studies [5, 17, 19, 27].

The epidemiological evidence outlined above has important implications for clinical surveillance: long-term surveillance of breast cancer patients should focus on the contralateral breast in order to detect an eventual second breast tumour as early as possible [30]. In absolute terms, the risk of a later contralateral breast cancer is substantial: in our study, it amounted to 7.2 and 6.1% within 15 years after diagnosis (conditional on the absence of competing causes of death) in patients whose first breast cancer was diagnosed before and after the age of 50, respectively (see Fig. 1). On the other hand, the patients who are cured from the initial cancer may be given the assuring message, that, despite frequently applied radiotherapy and/or chemotherapy, their risk of developing another malignant neoplasm outside the breast is not elevated compared to the general population, even in the long term.

As illustrated above, cancer registry studies on the occurrence of second primary neoplasms are of immediate interest for both aetiological research, as well as clinical practice. The main limitation of this study lies in the small numbers of second cancers even after 20 years of population-based cancer registration. Furthermore, overly restrictive data protection laws in the Federal Republic of Germany (FRG) hindered validation of the notifications to the registry and supplementation of the data base by more specific information on risk factors, diagnosis, and therapy. In order to take full advantage of the contributions that can be provided by cancer registration, extension of the population covered by reliable cancer registration is badly needed in the FRG, as well as a legal basis that allows the cancer registries to actively participate in analytical epidemiological studies, both on the regional as well as on the international level.

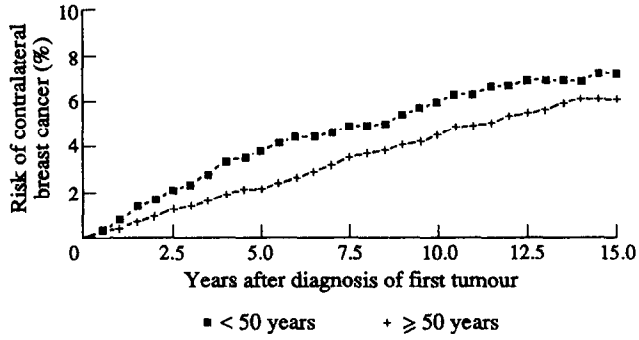

Fig. 1. Cumulative risk of contralateral breast cancer by age at diagnosis of the initial breast cancer and follow-up time, conditional on the absence of competing causes of death. Patients with simultaneous diagnosis of bilateral breast cancer are excluded from this analysis.

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Response of a Cancer Registry to Reports of Disease Clusters

Will D. King, Gerarda A. Darlington, Nancy Kreiger and Gordon Fehringer

A protocol has been developed to investigate and report perceived clusters of cancer using a population-based cancer registry. The protocol comprises a series of steps which lead to assessment of the cluster's importance on the basis of three criteria: (1) statistical evidence of clustering; (2) documentation of the existence of exposure to a carcinogen; and (3) biological plausibility of the relationship between the exposure and the cancer of interest. The evaluation of these criteria results in one of three recommendations: further study, surveillance only, or no action. The protocol provides a systematic approach for investigation, makes efficient use of available cancer registry data, and responds to public concerns. The protocol is demonstrated by its application to an inquiry concerning an apparent excess of lung cancer in a small Ontario town and the possible role of radon gas exposure. The public health importance and limitations of addressing perceived disease clusters are discussed.
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INTRODUCTION

In 1990, the Ontario Cancer Treatment and Research Foundation (OCTRF) received over 150 inquiries concerning the occurrence of cancer. Most of these were addressed with existing cancer statistics derived from the Ontario Cancer Registry (OCR); a number, however, concerned potential cancer clusters, a type of inquiry for which no formal response guidelines existed. As a result, a protocol was developed to investigate reports of perceived cancer clusters using registry data. The investigation of such reports provides an important public service and has the potential to identify environmental risk factors for cancer. This paper describes the protocol which has been developed and discusses its application to a recent citizen concern.

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SUBJECTS AND METHODS

The development of the cancer cluster protocol was based on existing informal procedures of the OCTRF, a review of protocols used by other disease control agencies [1–4], and consideration of available resources. This protocol is distinguished from others by its use of incidence data derived from a cancer registry rather than the informant. The OCR contains records on residents of Ontario diagnosed as having cancer since 1964. This resource permits us to carry out temporal and geographical investigations of cancer incidence in an expeditious and non-invasive manner.

Protocol

The cluster protocol is applied to those inquiries which concern associations among cancer cases characterised by: (i) a defined geographical area and/or time period, (ii) a localised environmental exposure, (iii) an institutional exposure (e.g. hospital, school), or (iv) an occupation. The protocol comprises six steps, as follows.