ORIGINAL ARTICLE

Suicide in breast cancer patients: An individual-centered approach provides insight beyond epidemiology

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Abstract
Background. Epidemiologic studies have identified increased suicide rates among breast cancer (BC) patients. The population-based approach, however, has considerable methodic shortcomings. None of the studies have been carried out in a prospective manner and none reported suicide rates from a country in which physician-assisted suicide (PAS) is legal. *Patients and methods.* All cases recorded by a prospective Swiss BC database during a 17-year period (1990–2006; n = 1165) were analyzed. Using an individual-centered approach, the cases of women who committed suicide are reported according to the psychological autopsy method. *Results.* In six patients (0.5%; 5.1/1.000 patients), suicidal death was identified. In four patients, suicide was committed during late stages of metastatic BC. In two cases, comorbid conditions were associated with suicide. Three women chose PAS. *Conclusion.* The individual-centered approach is a well-suited innovative concept to increase the knowledge regarding the relationship between cancer and suicide. We found a two to seven times higher suicide rate than those reported in epidemiologic studies. The population-based approach can barely elucidate the immense variety of one of the most personal decisions: the act of intentionally ending one's own life. These studies suffer from systematic failure of analysis since they did not a) consider the potential confounding role of comorbid medical and/or psychiatric conditions, and b) report in which disease stage suicide was committed, since the decisive disease-related event whether and when metastatic disease occurred was not recorded. Furthermore, epidemiologic data stems from countries in which PAS is prohibited and therefore not included in official statistics. This grey area of medicine accounts for a greater scope of underreporting than had previously been assumed.

The epidemiologic studies on the base of large cancer survivor cohorts have consistently identified increased suicide rates among patients with cancer [1–8]. The incidence of suicidal death in individuals with cancer in the US is approximately twice that of the general population [7]. The current European studies have demonstrated slightly lower risks with standardized mortality ratios of suicide between 1.35 and 1.9 [1,4,8]. The few which did calculate site-specific suicide rates correspondingly reported an increased risk of suicide among breast cancer patients [4,7–9].

Epidemiologic studies addressing the question of the relationship between cancer and suicidal death impress with an immense number of cases [1–9]. The statistical results of these studies are undoubtedly powerful and robust. In our opinion, they offer an interesting approximation of the problem. There remains, however, an essential question: how reliable is epidemiologic data which aims to quantify an event which is influenced by an enormous scope of individual factors and which is one of the most personal and intimate decisions of a human life: the act of intentionally ending one's own life. We think that in this particular field, the analyses of a prospective smaller database which is able to demonstrate individual suicide cases by an individual-centered approach (psychological autopsy) [10], can test the validity of epidemiologic studies (population-based approach) and add new insights. To our knowledge, our study is the first to follow this concept. Our data is of particular interest because it stems from a country in which physician-assisted suicide (PAS) is legal [11].

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Patients and methods

The prospective Basel Breast Cancer Database (BBCD) includes all newly diagnosed primary invasive breast cancer cases treated at the University Women's Hospital Basel, Switzerland since 1990. This institution comprises the largest breast center in the canton of Basel and represents the population of the region. For this study, data from patients up to and including 2006 was analyzed (n = 1193). With the exception of 28 patients who were lost to follow-up in the course of time (median follow-up time: 17 months, range 1–151 months), representing 2.3% of the database cohort, we were able to provide outcome information for all other patients. Of these patients, none had metastatic disease at the time of their last consultation and most were foreigners who had returned to their countries of origin. The remaining 1165 patients (median age at diagnosis: 61 years, range 26–95 years) were followed until death or, if they remained alive and disease free, for a maximum of 19 years. The mean follow-up duration after breast cancer diagnosis was 86.5 months (range < 1 months to 237 months). At the time of data collection in December 2009, the outcome data of patients still alive was not older than six months.

The BBCD collected disease-specific clinical, histo- and pathomorphologic features and treatment characteristics. It also includes data regarding personal and family history and outcome. The data was recorded continuously from the medical files. Approximately 30% of the patients, who were still alive, but no longer cared for in our institutional after-care program, are regularly contacted by telephone. For all patients who died during the observation period, there existed either official hospital reports or written/verbal communication from the treating general practitioner, such that reliable data regarding cause of death was available.

To report the cases of women who committed suicide, we used the psychological autopsy method. This technique is based upon a combination of interviews of those closest to the deceased and an examination of corroborating evidence from sources, such as hospital and general practice case-notes and criminal records. An assessment is made of the suicide victim's personality and mental and physical health using this information. The aim is to produce as full and accurate a picture of the deceased as possible while trying to understand why they killed themselves [10].

Data collection methods and study design were approved by the institutional review board (EKBB: 139/08).

Results

During the observation period, 456 of 1165 women died (39.1%). Of these, 264 patients had breast-cancer related deaths (57.9%), while 192 died of non-breast cancer diseases or other conditions (42.1%).

In six patients (0.5%; 5.1 per 1000 patients), suicidal death was identified. These six cases, including clinicopathologic characteristics of the primary carcinomas and course of cancer therapy, are described in detail below and summarized in Table I. In terms of age, tumor stage, primary treatment and date of initial diagnosis and death, no statistical significant differences between suicide cases and non-suicide patients of the total sample were found.

Case 1

This 40-year-old woman had been diagnosed with stage IIA (American Joint Committee on Cancer/International Union Against Cancer TNM Classification [12,13]) invasive lobular carcinoma in 1990. Fourteen years after initial diagnosis of the primary disease, extensive bone and lymph node metastases were diagnosed. For pain relief, metastatic lesions in the cervical and lumbar vertebral bodies were irradiated and endocrine therapy with anastrozole was administered. After a further eight months, the patient developed advanced local recurrence showing the clinical picture of an inflammatory carcinoma. After two lines of chemotherapy (capecitabine/docetaxel followed by epirubicin), a palliative mastectomy was performed. A third-line chemotherapy with vinorelbine could at first stabilize the disease; however, lung and hepatic metastases were later diagnosed. In the last months of her life, cutaneous metastases and severe dyspnea worsened the quality of her life, and in 2007, more than 16 years after the initial diagnosis of the primary disease and 30 months after diagnosis of metastatic disease, she chose PAS.

Case 2

This woman had been diagnosed with breast cancer in 1994 at the age of 60. Significant in her medical history was the diagnosis of severe depression associated with a histrionic personality disorder. Over the previous four years, she required several in-patient stays in psychiatric wards. She repeatedly expressed suicidal ideation. In the spring of 1994, she jumped from a height of 10 m. As a result, she suffered multiple fractures of the lower extremities, pelvis and spine; the left foot had to be amputated. In addition, she had paraplegic syndromes due to a cauda-conus syndrome. During the eight-month stay in different acute and rehabilitation centers, breast cancer was diagnosed. Since immediate surgical removal was not possible, neoadjuvant endocrine therapy with tamoxifen was initiated.

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Table I. Summary of characteristics of six breast cancer patients who committed suicide.

	Case 1	Case 2	Case 3
Primary breast cancer disease			
age at initial diagnosis	40	60	54
TNM classification	pT2 pN0 cM0	ypT1c cN0 cM0	pT2 pN3a cM0
TNM stage[1]	IIA	I	IIIC
Histological type, grading	Lobular, G3	Ductal, G2	Ductal, G3
HR status	ER- PR-	ER + PR +	ER- PR-
Kind of surgery	BCT + ALND	BCT	BCT + ALND
Adjuvant chemotherapy	No	No	Yes (epirubicin/ cyclophosphamid)
Adjuvant endocrine therapy	No	Yes (tamoxifen)	No
Adjuvant radiotherapy	Yes	No	Yes
Metastatic disease			
Recurrence occurred	Yes	No	Yes
Recurrence free survival (months)	169	n/a	7
Palliative chemotherapy, number of lines	Yes, 3 lines	n/a	Yes, 3 lines
History			
Psychiatric history	No	Severe depression, histrionic personality disorder	No
Medical history	No	No	Colitis ulcerosa: minor symptoms, conservative management
Condition at time of suicide			
Age	56	60	55
Metastatic site at time of suicide	OSS, LYM, CUT, HEP, PLE, PUL	n/a	OSS, LYM, CUT, BRA
Cancer-related symptoms	Severe: pain, dyspnea	None	Moderate: pain, dizziness, nausea
Symptoms of illness independent of cancer	No	Severe depression	No
Survival after initial cancer diagnosis (months)	199	9	16
Survival after diagnosis of recurrence (months)	30	n/a	9
Mechanism of suicide	PAS	Jumping from height	Suicide by train

	Case 4	Case 5	Case 6
Primary breast cancer disease			
age at initial diagnosis	80	81	64
TNM classification	pT1c pN0 cM0	pT1c pN3a cM0	pT2 pN0 cM0
TNM stage[1]	I	IIIC	IIA
Histological type, grading	Ductal, G2	Lobular, G3	Ductal, G1
HR status	ER- PR-	ER + PR +	ER + PR +
Kind of surgery	BCT + ALND	Mastectomy + ALND	BCT + Sentinel lymph node biopsy
Adjuvant chemotherapy	No	No	No
Adjuvant endocrine therapy	No	Yes (tamoxifen)	Yes (tamoxifen)
Adjuvant radiotherapy	No	No	No
Metastatic disease			
Recurrence occurred	Yes	Yes	No
Recurrence free survival (months)	16	11	n/a
Palliative chemotherapy, number of lines	No	No	n/a
Palliative radiotherapy	No	No	n/a

(Continued)

Table I. (*Continued*).

	Case 4	Case 5	Case 6
History			
Psychiatric history	No	No	No
Medical history	Chronic renal disease (hemodialysis), anal cancer, cardiovascular disease,	Hypertension	Rheumatoid arthritis, obesity, thyroid cancer, cardiovascular disease, type 2 diabetes
Condition at time of suicide			
Age	82	83	66
Metastatic site at time of suicide	PUL	SKI, OSS	n/a
Cancer-related symptoms	Severe: pain, dyspnea	Severe: pain (cancer en cuirasse), lymphedema	None
Symptoms of illness independent of cancer	No	No	Severe: analgesic-resistant pain and nearby complete immobility due to rheumatoid arthritis
Survival after initial cancer diagnosis (months)	17	29	25
Survival after diagnosis of recurrence (months)	0.5	18	n/a
Mechanism of suicide	Discontinuation of hemodialysis	PAS	PAS

n/a, not applicable; G, Grade; HR, hormonal receptor; ER, estrogen receptor; PR, progesterone receptor; BCT, breast-conserving therapy; ALND, axillary lymph node dissection.
Notation of distant metastatic sites: BRA, brain; HEP, hepatic; LYM, lymph nodes; OSS, osseous; PLE, pleura; PUL, pulmonary; SKI, skin.
[1]AJCC (American Joint Committee on Cancer)/UICC (International Union Against Cancer) TNM Classification [12,13].

After three months, the patient was operable and a simple tumorectomy was performed. Due to considerable restriction of mobility, adjuvant radiation could not be performed. Tamoxifen was continued postoperatively. In spring 2005, six weeks after discharge from the rehabilitation center and six months after breast cancer surgery, the patient died after intentionally jumping from the third floor of her house.

Case 3

This 54-year-old woman had been diagnosed with stage IIIC invasive ductal breast carcinoma in 1996. Five months after completion of adjuvant chemotherapy, bone (thoracic vertebrae) and supraclavicular lymph node metastases were found. In the further course of palliative treatment, radiation and three lines of chemotherapy were administered. Nine months after the initial confirmation of distant metastases, additional skin and brain metastases were diagnosed. Two weeks after receiving this information, she committed suicide by jumping in front of a train. She left a farewell letter to her family.

Case 4

This 80-year-old woman had been diagnosed with stage I invasive ductal carcinoma in 2001. After breast-conserving therapy (BCT) with axillary lymph node dissection (ALND), no adjuvant therapy was administered at patient's request and due to multiple comorbidities. Remarkable in the medical history were a further malignancy (2000: anal cancer; radiation therapy), cardiovascular disease (1998: myocardial infarction), type 2 diabetes mellitus and chronic kidney disease caused by glomerulonephritis. Since 1999 hemodialysis had been required. Sixteen months after initial diagnosis of primary breast cancer the patient developed dyspnea and further diagnostics showed massive lung metastases. The patient declined any antineoplastic therapy. Faced with increasing symptoms of dyspnea, she decided to stop dialysis, knowing full well that this would lead to death. The patient died six days after this decision.

Case 5

This 81-year-old woman had been diagnosed with stage IIIC invasive lobular breast carcinoma in 2003. She was surgically treated with mastectomy and ALND. Adjuvant chemotherapy and radiation were declined by the patient. Adjuvant endocrine therapy with tamoxifen was administered. Eleven months after initial diagnosis, hormonal receptor negative chestwall and axilla recurrence was diagnosed and a locoregional radiation was performed. In the further course, the patient developed a further chest wall recurrence which was surgically treated. Two months after surgery, a third chest wall recurrence occurred;

bone metastases were also found at the same time. The chest wall recurrence showed massive progress and within three months severe lymphedema and painful tumor spread over her entire upper body ("cancer en cuirasse") had developed. Due to the fulminant course, further operative and radiooncologic management was not possible; the patient continued to refuse chemotherapy. In 2006, 18 months after the initial diagnosis of local recurrence, she chose PAS.

Case 6

This obese woman, who was diagnosed with breast cancer in 2006 at the age of 64, had a multitude of medical problems. In 1980, thyroid cancer was surgically treated; in 2005 she suffered a myocardial infarction; type 2 diabetes mellitus was a chronic affliction for years. Yet the greatest cause of suffering for this woman was progressive rheumatoid arthritis which she had since the age of 35. Despite multiple and intensive treatment including several orthopedic surgical procedures, analgesics, steroids and disease-modifying antirheumatic drugs, she developed progressive joint destruction. She had been restricted to a wheelchair since 2002. In 2006 she was diagnosed with stage IIA invasive ductal breast carcinoma and was surgically treated with BCT and sentinel lymph node biopsy. Adjuvant radiation was not possible due to limited mobility. Tamoxifen was initiated and regularly taken. In the subsequent two years, the rheumatoid arthritis was further progressive, such that even minimal movements were hardly possible due to therapy-resistant pain and stiffness. In 2008, 25 months after the breast cancer diagnosis, she chose PAS and passed away surrounded by her family and friends.

Discussion

How attributable are suicides in breast cancer survivors to breast cancer?

The authors of some epidemiologic studies concluded that the use of psychosocial interventions in patients with cancer can make a positive impact on quality of life and might reduce suicide [4,5,7,9]. These statements reflect the opinion that the observed suicides in cancer patients have a more or less direct correlation with the disease. This interpretation, however, cannot be supported in all cases. Although we know that suicide is a multi-determined act and the search for a single explanatory factor is often too simplistic, we think that in two of the six suicide cases in our cohort, there is strong evidence that the cancer hardly contributed to the patient's decision to end her life. In both cases, long-standing psychiatric (Case 2: severe depression with repeated suicidal tendencies)

or physical (Case 6: progressive arthritis associated with severe restrictions of mobility and analgesic-resistant pain) illness, which was existent many years before the cancer diagnosis, must be recognized as the triggering factor for suicide. When one wants to describe the relationship between cancer and suicide on the basis of large databases, suicide patients such as the above mentioned should be identified and considered separately in the analyses. An uncensored inclusion of these cases could possibly lead to inappropriate interpretation of the data. Up to now, no epidemiologic study has been able to address this problem sufficiently and did not consider the potential confounding role of comorbid medical and psychiatric conditions.

On the other hand, the existence of breast cancer, and in particular of a metastatic situation, can have a strong impact on the handling of other medical conditions, a fact that also remains largely undetected in epidemiological studies. In Case 4, the patient clearly asked to stop hemodialysis – and therefore to die – not because dialysis had become futile in her eyes but as a means to escape the end stage of breast cancer. In this specific situation, we believe that it is justified to regard death as a form of suicide, although, legally speaking, death caused by cessation of dialysis is not suicide but withdrawal of treatment [14,15].

Are there particular high suicide rates in the period immediately after diagnosis?

Two decisive disease-related events seem to be important. On one hand, there is the initial diagnosis. In the following time period, many patients go through a crisis trying to cope with the fact that they have a potentially life-threatening disease. Some authors found that patients were most vulnerable to suicide in the period immediately after diagnosis [4,8,16]. However, our data did not support these findings. There was only one patient who committed suicide within the first year after initial diagnosis (Figure 1). In this particular case (Case 2), preexisting long-lasting psychiatric illness heightened by orthopedic and neurologic disability resulting from the previous suicide attempt, and not the cancer diagnosis, must be considered as the key factor for suicide.

The second decisive disease-related event, and probably the even more difficult situation, is when distant metastases are diagnosed and the patients are faced with the fact of an incurable disease. In addition to this mental distress, most patients develop severe cancer-related physical complaints in the further course of the palliative situation. Epidemiologic studies, however, are not able to consider
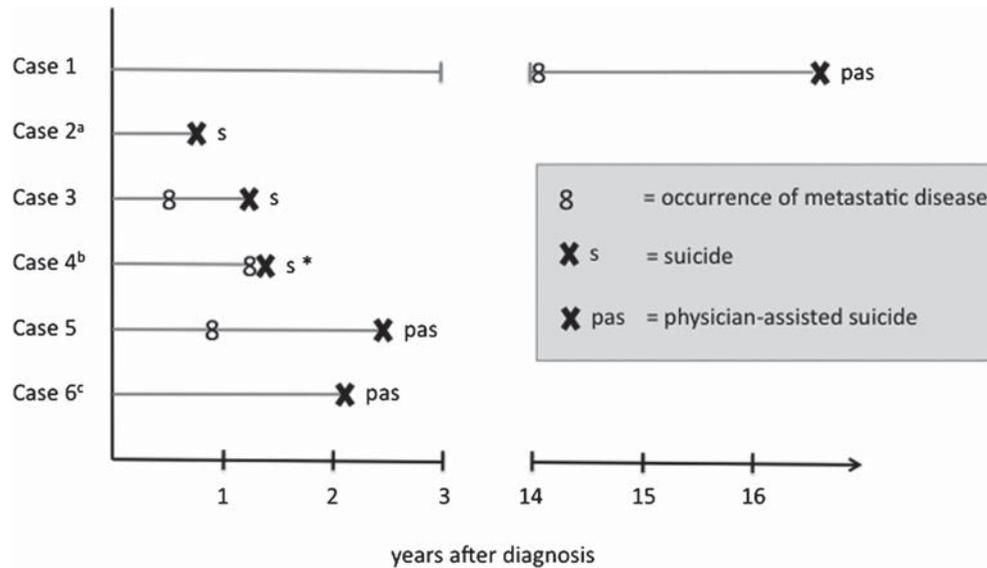
Figure 1. Course of events in six cases of suicide after breast cancer diagnosis. [a]Preexistence of severe depression and personality disorder with repeated suicidal intentions; [b]Preexistence of chronic kidney disease and dependence on hemodialysis; *voluntary death after request to stop hemodialysis; [c]Preexistence of severe progressive rheumatoid arthritis.

this essential event during the course of disease. When recording patients, they do not differentiate between those who were free of disease after a curative therapy at the time of suicide and those who were in a prefinal situation. We think that this is a severe limitation of all epidemiological studies evaluating the risk of suicide.

It's our opinion that the awareness of having an incurable disease is a relevant factor for suicide in breast cancer patients. In our cohort, four of six patients who committed suicide had metastatic disease in a far advanced situation with a presumed survival of a few weeks. Such circumstances can only be investigated by psychological autopsies [10,17], either retrospectively or using a prospective data collection design as we applied.

We hypothesize that the discovery of particularly high suicide rates found in the time period immediately after initial diagnosis [4,8,16] arises from a systematic bias. The date of initial diagnosis is an invariable event and all suicides in the next months can be clearly associated with this date. The point of time in which metastases occurs, however, is, particularly in breast cancer, considerably variable in the course of time. Due to the fact that this event is not even recorded, suicides after this event cannot be attributed accordingly. A peak of some suicide cases shortly after initial diagnosis and the distribution of the majority of cases over a long period might lead falsely to the conclusion that suicide rates are higher shortly after initial diagnosis. Hem et al. found that, in contrast to other cancer entities, the risk among breast cancer patients was significantly elevated five or more years after diagnosis and

explained this observation with the unpredictable course of the disease [4].

The role of underreporting suicide, particularly in countries in which physician-assisted suicide (PAS) is illegal

The general problem concerning validity of suicide statistics is well known. In all databases evaluating suicides, there exists an inherent and unavoidable misclassification bias due to a non-accurate ascertainment of suicide which tends to be underreported as a cause of death [18]. This can partly be explained by the fact that suicide is often difficult to distinguish from other causes of death such as homicide and accidental death. We think that particularly in countries where PAS is not authorized by the law in force, there might be a substantial bias in the assessment of suicide in cancer survivors, because some suicide cases in late stages might not be classified accordingly.

From epidemiologic studies evaluating suicides among cancer patients, only two studies which analyzed data from the Cancer Registry of Norway, reported seven different methods for suicide (poisoning, hanging/strangulation, drowning, firearms/shooting, cutting/stabbing, jumping from heights, and others) [1,4]. Notably, "physician-assisted suicide" was missing in their list; this is not surprising as this procedure is illegal in Norway.

In our report, half of the patients who committed suicide (Cases 1, 5 and 6) chose a PAS supported by a registered private right-to-die organization. All of these women suffered from severe physical and

mental distress caused by a devastating situation in which few medical measures could promise any relief. In one case, there was a woman who had a progressive severe chronic arthritis for more than 20 years and was tired of a life, in which even very restricted forms of mobility were associated with considerable therapy-resistant pain. In the two other PAS cases, patients suffered from severe cancer-related symptoms, in particular the one who developed a massively painful, necrotizing and foul-smelling locoregional recurrence covering nearly the entire upper body ("*cancer en cuirasse*", Case 5). It must be noted that a prefinal situation did not exist in any of these cases, so these patients were not yet in the stage where the administration of analgetics and sedatives with the aim to alleviate symptoms is sometimes likely to shorten life by a few hours as a side effect (*indirect active euthanasia*) [19]. In both cases, without PAS, a survival of several weeks was a realistic expectation.

It is known that also in countries where PAS is prohibited, it still takes place in selected situations where doctors with a long-term trusting relationship with the patient, will respect and support the expression of personal autonomy in hopeless and agonizing late stage diseases [19–21]. In this grey area of medicine, these physicians would be reluctant to classify an intentional overdose of analgetics and sedatives as suicide, since the diagnosis of an extraordinary death means that medicolegal investigations, which could expose an illegal act, are mandatory.

Most authors of epidemiologic studies describe misclassification bias and potential underreporting as a possible limitation of their data, but do not believe that this influences the validity of their data significantly [1,4,7–9]. We do not support this assessment. We believe that in large databases, which can rely only on computerized codes (population-based approach), a relevant number of suicide cases remain undetected which might have been identified by an individual-centered approach where it is able to follow individual biographies. In this manner, we know that in at least one case of our cohort, the cause of death was not officially coded as a suicidal act but as renal failure (Case 4). Furthermore, we assume that the three cases where the patients chose PAS would not have been coded as suicide in countries where this procedure lies in an illegal grey area and therefore do not appear in official statistics. This hypothesis is supported by a comparison of suicide incidence rates. In our database, we found 5.1 suicides per 1000 breast cancer patients (Table II). This number is considerably higher than the data from US and Scandinavian epidemiologic studies which calculated 0.4–2.4 suicide deaths per 1000 breast cancer patients [5,7,9] (Table II). When one excludes the cases (n = 4) where we presume that in other databases suicide would not have been recorded, we found a rate of 1.7/1000 patients which corresponds with the previously reported epidemiologic data (Table II). This comparison increases the possibility that our above mentioned hypothesis is correct.

Several studies demonstrated that suicide mortality among cancer patients has decreased over time relative to the suicide trend in the general population [2,4,16,22]. Improved treatment options and better communication of diagnosis are possible explanations of this finding. According to this, one might expect that our Swiss cohort, where breast cancer was diagnosed during a relatively recent 17-year period (1990–2006), should depict even lower suicide rates than the above-cited US and Scandinavian populations where the start of the observation period was considerably earlier (Scandinavia: 1950s and 1960s; USA: early 1970s). However, exactly the opposite is true.

Table II. Observed number of suicide among breast cancer patients in our study and in different population-based cancer registries in USA and Scandinavia.

Cancer registry, registration period	No. of suicides/no. of cases	Incidence of suicide per 1000 patients
BBCD: 1990–2006	6 / 1'165	5.1
BBCD: 1990–2006 (excluding Cases 1, 4–6)	2 / 1'165	1.7
US SEER program: 1973–2001 [5]	92 / 21'6913	0.4
US SEER program: 1973–2002 [7]	294 / 417'821	0.7
Schairer et al. [9]*		
All patients	836 / 723'810	1.2
US SEER Program: 1973–2001	245 / 375'797	0.7
Sweden: 1958–2001	241 / 153'902	1.6
Denmark: 1971–1999	166 / 68'045	2.4
Finland: 1953–2001	125 / 71'099	1.8
Norway: 1961–2000	59 / 5'967	1.1

BBCD: Basel Breast Cancer Database; SEER: Surveillance, Epidemiology, and End Results.
*Schairer et al. [9] restricted their analyses on patients who survived at least one year.

It is our opinion that the comparably high suicide incidence rates of the population analyzed in this study is also associated with the fact that in Switzerland, PAS is not only legal, but is also the subject of a comparably liberal and tolerant public discussion. We believe that suicide reflects only a small and quantitatively negligible tip of the iceberg of anxiety, mood disturbance, and potential other mental illness after a cancer diagnosis. Altogether, the analysis of a smaller cohort using an individual-centered approach has provided new insights to this field and partly questions the validity of the data from large epidemiologic studies. In the current state of research, further prospective studies using the method of psychological autopsies, which is probably the most direct technique currently available for determining the relationship between particular risk factors and suicide [10], are needed to gain further insight in the true backgrounds of suicide in cancer patients.

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