Risk Factors of Developing a Second Malignancy Following Treatment of a First Primary Breast Cancer

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Abstract

Background: Breast cancer is the most prevalent cancer among Iranian women, and is the fifth cause of cancer-related death in Iran. Most studies have reported an overall excess of 20–30% chance for a second primary cancer to develop in individuals with a first breast cancer. In this study, we evaluated different factors might have a role in increasing the incidence of a second malignancy after a first primary breast cancer in Iran.

Methods: We considered 980 breast cancer patients from three cancer research centers in Tehran, Mashad and Isfahan from Sep 1995 till Sep 2010.

Results: Overall, 94 second primary neoplasms observed. This analysis showed the existence of a modest excess in several neoplasms occurring after breast cancer. Some treatment related factors, including radiotherapy or mastectomy, had statistically significant relation with development a secondary cancer. However, sub-analysis failed to prove such a relationship.

Conclusion: Therefore, we can concluded that the risk of developing a second cancer is more dependent on genetic and environmental factors that caused the first primary cancer, rather than being dependent on type of treatment and other factors mentioned in this study.

Keywords: Breast cancer; Second primary; Therapy; Iran

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Introduction

Breast cancer is the most common cancer among women in many developed as well as developing countries. Most studies have reported an overall excess of 20–30% chance for a second primary cancer in individuals with a first breast cancer, not including contralateral breast cancer [1, 2]. A positive association between a first primary breast cancer and second primaries at other sites may be a result of shared risk factors: the inheritance of genetic mutations which confer a strong susceptibility to the relevant cancer; effects of therapy for the first cancer (radiotherapy, chemotherapy and hormonal therapy, etc); misdiagnosed metastases; environmental exposures that increase the risk of both cancers; hormonal factors; or chance [2, 3].
Breast cancer is the most prevalent cancer among Iranian women, and is the fifth cause of cancer-related death in Iran after gastric carcinoma [4].
Studying the prevalence of a second primary cancer after breast cancer is of outmost importance, as breast cancer is a very common malignancy and many affected individuals are expected to have a long-term survival. Therefore, it is important to know whether a survivor of breast cancer has an increased, decreased, or unchanged risk of developing a second cancer, in order to take those possibilities into account in follow-up visits. In this study, we aimed at

determining the incidence of second primary cancers in breast cancer patients in Iran.

Materials and Methods

The data was collected from the files of three surgeons from three hospitals in Tehran, Isfahan and Mashad from Sep 1995 till Sep 2010. Files with so much missing or inconsistent information were excluded from the study (although in almost all the files some data were missing). Male patients as well as patients who had metastatic disease or another known primary cancer at presentation or within three months after the first cancer were also excluded from the study. A total of 980 cases were included in the study. Apart from contralateral breast cancer that might have had a similar pathology to the primary cancer, we defined a new primary tumor as a tumor that had developed at a different anatomical site and with a different histological type from the first tumor, or as stated explicitly as being a new tumor by the treating clinician. Reliability of the findings was confirmed by the extent of available histologic diagnosis which was present in more than 90% of cases. Therefore a metastasis unlikely has been confused with a second primary tumor. Among these 980 breast cancer patients, 94 (9.5%) developed a second malignancy. To define the control group, adjustments were made for stage and mean duration of follow up. For each patient with a secondary cancer (case group) controls were chosen from the remaining 886 patients. For each patient in case group, we included control patients with the same stage disease (stages I, II or III based on TNM staging) whose follow up period was within ±6 months from the case patient. In this way, for each patient, 1-3 matched controls were found, and finally, 94 case patients and 202 control patients were included in the study.

Results

Among 980 cases, 94 (9.5%) developed a second cancer, including contralateral breast cancer. Mean time of developing a second cancer following the diagnosis of the primary breast cancer was 65.8±14.6 months. The frequency of the second malignancies is shown in Table 1.

As can be seen in Table 1, the most common type of secondary malignancy that has occurred after a first primary breast cancer, is the cancer of contralateral breast, followed by non-melanoma skin cancer and cancers of uterine and ovary. Based on the data from Iranian Cancer Registry, the incidence of developing a cancer of any type and origin is about 1 in 1000 among Iranian women. However, as can be seen in Table 1, the incidence of developing a second cancer among women with a history of breast cancer is much higher than that of general population. For instance, while the ASR (Age Adjusted Rate) of developing breast cancer is 33.21 among 100000 women in general population, women of our study developed breast cancer at the rate of 35 per 1000, which means that incidence of breast cancer in these women is 100 times more than that of general population. The similar figure is true for other types of cancer too.

Table 2 shows the description of patients in case and control groups. As can be seen in the Table, there was no difference between age and mean duration of follow up between the two groups.

Table 1. Second malignancies

Site of second cancer	Frequency (percent)	ASR
Breast	35 (37.2%)	33.21
Skin	11 (11.7%)	15.77
Endometrial	11 (11.7%)	2.5
Ovary	7 (7.44%)	4.25
Colorectal	5 (5.31%)	11.12
Cervix	3 (3.19%)	2.61
Esophagus	3 (3.19%)	7.77
Thyroid	2 (2.1%)	4.47
Brain	2 (2.1%)	3.09
Salivary glands	2 (2.1%)	0.5
Lymphoma	2 (2.1%)	2.63
Sarcoma	2 (2.1%)	Not available
Kidney	1 (1.06%)	1.81
Bladder	1 (1.06%)	3.78
Chordoma (sacral spine)	1 (1.06%)	Not available
Pancreas	1 (1.06%)	1.07
Lung	1 (1.06%)	3.55
Small intestine	1 (1.06%)	Not available

ASR: Age Standardized Rates of cancer among Iranian women in 2008 (Number of cases per 100000 women, collected from Iranian Cancer Registry)

Post-menopausal status was associated with more chance of developing a second cancer in our study. Type of surgery was also significant between the two groups; patients by history of mastectomy had a greater chance of developing a secondary cancer. Secondary malignancies also more occurred in patients who had only radiotherapy as the adjuvant treatment.

Discussion

Similar to majority of previous studies, our study also showed the existence of an excess in several neoplasms following a diagnosis of breast cancer.

The prevalence of multiple primary malignancies after a first primary cancer seems to be increasing. This is believed to be –mainly– due to the effect of shared risk factors, such as: environmental exposures that increase the risk of both cancers; hormonal factors; similar genetic mutations that can lead to different cancers; potentially carcinogenic side effects of the therapy for the first cancer (radiotherapy, chemotherapy and hormonal therapy, etc); misdiagnosed metastases; or chance [2, 3]. However, this can be partly due to the fact that people with a cancer history are visited more frequently by medical professionals than other people, and modern diagnostic modalities have enabled physicians to diagnose more cancer cases. Furthermore, this increase in multiple primary cancers could be to some extent due to the fact that many breast cancer patients live long enough to develop a second primary cancer. Breast cancer is the most common malignancy among women in many parts of the world, and the number of survivors has been increasing steadily during the past decades, mainly because of earlier diagnosis as well as improvements in therapeutic measures. As a result, the number of breast cancer patients who develop a second malignancy has also increased recently. Results of Dong et al. study on more than 630,000 patients in Sweden with a primary cancer (any primary in any part of the body) showed that compared with the general population, male and female patients were at risk of 1.3 and 1.6 for developing a second cancer, respectively. Of the male second primary cancers, 51% followed cancer of the prostate, urinary bladder, colon and skin (non-melanoma), whereas 53% of female subsequent cancers occurred after cancer of the breast, endometrium and cervix [5].

Results of a large study on more than 525,000 women with a primary breast cancer showed that these patients have a 25% increase in the risk of developing a new primary non-breast cancer in comparison with women without cancer [2].

Table 2. Description of patients in case and control groups

Patients' characteristics		Case group	Control group	P- value
Mean age (years)		50.2 ± 8.3	56.4 ± 11.2	0.05
Mean follow up (months)		73.7 ± 54.8	74.1 ± 53.8	0.18
Menopausal status[1]	Premenopausal	71%	76%	0.003
	Postmenopausal	9%	0%	
	Missing data	14%	18%	N/A*
Positive family history[2]	First degree	12%	7%	0.4
	Second degree	3%	9%	
	First or second degree[3]	17%	0%	
	Negative family history	41%	60%	
	Missing data	21%	18%	N/A
Type of surgery	Breast conserving surgery[4]	16%	28%	0.018
	Mastectomy[5]	73%	55%	
	Missing data	5%	11%	N/A
	Chemotherapy only	9%	13%	

Treatment [6]	Radiotherapy only	17%	3%	0.002
	Both chemotherapy and radiotherapy	60%	60%	
	None	8%	18%	0.035
	Missing data	0%	0%	N/A
	Hormone Therapy	65%	63%	0.75
Recurrence[7]	Local and/or distant	23%	17%	
Hormone receptor status	Estrogen receptor positive	63%	66%	0.18
	Progesterone Receptor positive	71%	77%	0.17
	Her 2 positive	25%	20%	0.76

1- In majority of cases, no lab test was asked and the menopausal status was defined by history taking and patients' age.
2- Positive history of any cancer, excluding non-melanoma skin cancer.
3- Data was written as "positive family history" in the file without mentioning the exact relationship.
4- Including all types of surgery in which the whole breast is not removed.
5- Including all types of mastectomy.
6- Treatment rather than the surgery. Neoadjuvant or adjuvant treatments are categorized in the same group.
7- Including both local and/or distant recurrence.
*N/A: not applicable

In our study, 9.5% of patients with a first breast cancer developed a second primary malignancy, which is similar to the rates reported in many previous studies.

Similar to majority of previous studies, we also found that the most common second primary cancer after a primary breast cancer is the cancer of contralateral breast. The high incidence of cancer in the second breast may be expected since carcinogenic factors which have induced malignancy in one breast may also exert a similar influence on the remaining mammary tissue [6].

Following the contralateral breast cancer, the skin cancer is common. All cases of skin cancer in our study were non-melanoma. Many studies exclude non-melanoma skin cancer because of known under-reporting [3]. Among cases of skin cancer in our study, only 2 cases occurred in the radiotherapy field area, and 9 other cases occurred in regions similar to that of normal population, including scalp and face.

Similar to previous studies, after cancers of contralateral breast and skin, the most common cancers that developed in breast cancer patients were gynecological and gastrointestinal cancers.

Data from Iranian Cancer Registry shows that the most common cancers among Iranian women based on annual incidence include breast, skin, colorectal, stomach, esophagus, hematologic, thyroid and ovary [7].

Difference in the menopausal status of patients between two groups was statistically significant, with more cases of second malignancy in women who were post-menopausal at the time of diagnosis. To our best knowledge, there is no robust data in the literature to show that menopausal status has any relationship with developing a second cancer. As eliciting the data regarding menopausal status was based on history taking in majority of cases without any lab tests, it is possible that many women in perimenopausal period exist in both pre-menopausal and post-menopausal groups. As a result, this data can be quite inaccurate.

Similar to previous studies, young women in our study tended to develop more second primary cancers compared to older women. This can be due to a genetic susceptibility, as individuals with a genetic predisposition tend to develop cancers at younger ages [3]. However, it is also possible that the overall significant decrease in tumors reported after an older diagnosis of breast cancer may be due to under-ascertainment. It is conceivable that medical surveillance is reduced in older patients. Older women may not have such aggressive treatment as the younger cases and so might develop fewer treatment-related cancers [3].

Positive family history in some studies has been considered to be a risk factor for developing a second cancer. They argue that the same reasons that can cause the first cancer in an individual with a positive family history of cancer can result in the

development of a second malignancy. In our study, however, no relation was found between the positive family history and development a second cancer.

Hormonal status of the breast cancer is a predictive as well as prognostic factor for treatment and recurrence of breast cancer; however, it has not been shown to have any relation with causing a second primary cancer. Status of Her-2 neu and estrogen and progesterone receptors had no relation with the development of a second cancer in our study. In another analysis, we considered only breast cancers as the second malignancy, and still the status of Her-2 neu and estrogen and progesterone receptors was not statistically different between the case and control groups.

Type of treatment, in many studies, has been shown to have a relationship with the development of a second cancer. Chemotherapy influences the risk and rate of secondary malignancies in high-risk populations. The alkylating agents, topoisomerase inhibitors, and anthracycline agents pose the highest risk of initiating carcinogenesis. Normal cells that are especially sensitive to chemotherapy and most likely to begin carcinogenesis include those of the bone marrow, hair follicles, and the epithelial cells of the gastrointestinal tract. Therefore, the development of secondary hematologic cancers such as leukemia and lymphoma pose the greatest risk to cancer survivors [8].

Rubino et al. studied the role of initial treatment on risk of a second primary neoplasm after breast cancer treatment. By excluding second primary breast cancer and non-melanoma skin cancer, 4.4% of their patients developed a second primary neoplasm one year after completion of the treatment. The greatest increase in the relative risk concerned soft tissue cancers followed by leukemia, melanoma, kidney, ovary and uterine tumors. The number of second malignancies was significantly higher in patients who had received radiotherapy, and they concluded that there is an increased risk of second malignancies in women treated for a breast cancer, particularly in those who are younger at the time of treatment. They also concluded that radiotherapy may play a role in the onset of these second lesions [9].

However, there is no general agreement on the role of radiotherapy in inducing malignancies. For instance, in a study done on more than 1000 patients, after 15 years of follow-up, no difference was observed between early stage breast cancer patients who were treated with lumpectomy and radiation therapy compared to similar cases who were treated by mastectomy without radiation [10].

Table 3. Type and frequency of the second cancer in patients who have had radiotherapy only

Type (site) of cancer	Frequency (percent)
Contralateral breast	7 (41.1%)
Skin	3 (17.6%)
Ovary	1 (5.8%)
Retroperitoneal sarcoma	1 (5.8%)
Rectum	1 (5.8%)
Colon	1 (5.8%)
Thyroid	1 (5.8%)
Esophagus	1 (5.8%)
Uterine	1 (5.8%)

Several studies have demonstrated that radiotherapy is a significant risk factor for the development of soft tissue sarcomas, in particular angiosarcomas, after breast cancer treatment [2, 11]. There are also some concerns regarding the cancer of contralateral breast following radiotherapy for the other breast. However, several studies have shown that the risk is negligible [12]. In our study, chemotherapy (with or without radiotherapy) did not seem to increase the risk of a secondary malignancy. Patients who had not received any adjuvant therapy showed less incidence of a secondary cancer, while patients who had received only radiotherapy showed increased rate of developing a second malignancy. However, if we consider all cases of radiotherapy (including those who have had chemotherapy as well), this statistically significant difference disappears. We studied the types of second cancers in patients who have had only radiotherapy. Table 3 shows the types of secondary cancers in this group.

Table 4.Types of adjuvant treatment

Surgery / Adjuvant treatment	BCS	Mastectomy	P-Value
Radiotherapy only	11.4%	10.9%	NS*
Chemotherapy only	11.3%	11.7%	NS
Both treatments	65.9%	67.2%	NS
No treatment	11.4%	10.2%	NS

*NS: not significant

As can be seen in Table 3, the most common secondary malignancy occurred in the contralateral breast. Among 3 cases of skin cancer, only one occurred in the radiation field, and the other 2 developed in face and scalp. Other cancer that has occurred within the close proximity of the radiation field is thyroid cancer. In our study, there were 2 cases of thyroid cancer. Both patients had received radiotherapy as part of their treatment (one with chemotherapy and the other without). By some authors, thyroid cancer is regarded as a radiation inducible cancer, however, this is controversial [2, 3]. Many studies have shown that the risk of thyroid cancer is not higher among breast cancer patients treated with radiotherapy compared to those didn't treat with radiotherapy [13, 14]. Therefore, it seems that having radiotherapy in adulthood may not affect the risk of thyroid cancer to any great extent [2].

All other mentioned malignancies in Table 3 have occurred in sites that are unrelated to radiotherapy. Therefore, apart from slight possible increase in the chance of contralateral breast cancer that many authors consider negligible, radiotherapy in our study did not seem to increase the incidence of developing a second cancer.

Type of surgery was different in two groups and our study showed that a second cancer occurred more in the women who had undergone a mastectomy, compared to women with Breast Conserving Surgery (BCS).Type of surgery has always been studied as whether or not one type is more associated with local recurrence, and to our best knowledge there is no data indicating that one type of surgery might be related to increasing the risk of a second cancer. Table 4 shows the type of adjuvant therapy that the patients received following the surgery. As can be seen in the Table, there is no significant difference between the types of adjuvant treatment between the two groups. Therefore, presence of more cases of secondary malignancy in mastectomy patients in our study is probably related to other factors that are elusive.

Conclusion

Our study found that there is an excess in several neoplasms following a diagnosis of breast cancer, and women with breast cancer are at greater risk for developing a second cancer following the treatment. However, our study did not show that any type of treatment would have a dramatic influence in inducing a second malignancy. By looking at the Iranian Cancer Registry [7], it can be found that the type and site of second malignancies in our study is very much similar to the type and site of cancers that occur annually in general population. Therefore, we may be able to conclude that the risk of developing a second cancer, more than being dependent on type of treatment and other factors mentioned in this study, is dependent on genetic and environmental factors that caused the first primary cancer.

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Conflict of Interest

We certify that there is no conflict of interest in this study.

Authors' Contribution

Ahmad Rezazadeh Mafi contributed in designing the study, did the literature review, and wrote the paper.
Shadi Babazadeh, Fatemeh Homaee Shandiz and Morteza Tabatabaeefar contributed in collecting the data, data entry and analysis.
Zahra Razzaghi helped in collecting the data, data entry and analysis, and designing the study.
Mohammad Esmaeil Akbari designed the study, read and approved the final manuscript. Sara Sobhi contributed in writing the manuscript.

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