Does Prophylactic Radiotherapy to avoid Gynecomastia in Patients with Prostate Cancer increase the risk of Breast Cancer?

Running title: Does RT to the breast buds increase BC risk?

Summary (74 words)

Nordic patients with prostate cancer receive prophylactic radiotherapy to the breast buds to avoid gynecomastia when treated with antiandrogen monotherapy. In this study with data from the Norwegian Cancer Registry, we did not find increased risk of breast cancer (BC) in irradiated patients compared to non-irradiated patients. It is noteworthy that in the RT group, there were two cases of malignant phyllodes breast tumor, an extremely rare type of BC associated with gynecomastia.

Abstract

Purpose

Prostate cancer (PC) patients treated with antiandrogen monotherapy are offered prophylactic radiotherapy to the breast buds (PRT) to avoid gynecomastia. The aim of this study was to evaluate whether the risk of breast cancer (BC) in men with PC as their first cancer diagnosis, was influenced by PRT.

Methods and Materials

From the Norwegian Cancer Registry we collected data on all patients with PC as their first cancer diagnosis diagnosed between 1997- 2014. We registered all radiotherapy given to the patients in the same period, and the occurrence of BC diagnosed 3 months or more following the PC diagnosis. The histopathological diagnoses of all BC cases were collected. Subdistribution hazard ratios (SHR) for the risk of BC in PRT and non-PRT treated patients were estimated. A standardized incidence ratio (SIR) for BC was calculated by comparing our cohort to the standard male population.

Results

We analyzed 59 169 patients with PC, whom 7864 (13.3%) had received PRT. Median follow-up time was 4 years. Three of 12 men diagnosed with BC had received PRT, and two of three were phyllodes tumors. The risk of BC was not statistically significantly different in patients given RT as compared to the non-RT patients, SHR 1.62 95% CI 0.41-5.62, adjusted for age and time of diagnosis. SIR was 0.996 95 % CI 0.57-1.75.

Conclusions

In this registry based study, we did not find an increased risk of BC in PC patients treated with PRT. The number of BC cases in our study was low, and the risk of secondary breast cancer following PRT seems to be negligible. The incidence of BC may, however rise with additional follow-up. It is noteworthy that two patients who had been treated with PRT were diagnosed with malignant phyllodes tumor, an extremely rare type of BC associated with gynecomastia.

Introduction

Antiandrogens are well established treatment for prostate cancer (PC). In the Nordic countries antiandrogen monotherapy has been used in the adjuvant setting after radical radiotherapy (RT) for PC as an alternative to medical castration [1]. Recently, Shipley et al. reported that the addition of 2 years of antiandrogen treatment improved overall survival (OS) in patients undergoing salvage RT due to relapse following radical prostatectomy [2]. Moreover, antiandrogen monotherapy may be beneficial in patients with locally advanced PC not suitable for RT [3]. In 1998 Tyrell et al. showed that bicalutamide was inferior to castration only by a median of 42 days with respect to OS in metastatic PC patients, with less side effects and superior quality of life [4]. Although controversial, antiandrogen monotherapy may thus be an alternative in patients with metastasis unwilling to undergo castration.

A common side effect of antiandrogen monotherapy in men is mammary gland proliferation (gynecomastia) with a reported incidence of 40- to 80% [5, 6, 7, 8]. Gynecomastia frequently causes tenderness and may be a cosmetic problem that influences the willingness to continue antiandrogen treatment. In a study reported by Wirth et al., 16.8 % of PC patients treated with antiandrogens withdrew from the medication because of gynecomastia [9]. Consequently, prophylactic radiotherapy to the breast buds is applied to avoid antiandrogen induced gynecomastia and approximately 550 Norwegian men are treated with prophylactic RT each year[8, 10, 11]. It is not recommended to treat patients on low doses of antiandrogens with prophylactic RT.

Gynecomastia is, however, a benign condition and the benefits of prophylactic RT to the breast buds must be weighed against the risk of serious radiation induced long-term effects. In theory, prophylactic RT may both increase and reduce the risk of male breast cancer (BC). Ionizing radiation may increase the cancer risk, possibly enhanced by increased cell proliferation induced by antiandrogens. The relatively high dose applied in prophylactic breast bud RT (10-15 Gy), often given in a single fraction, may reduce local cell proliferation in the male breast and sterilize malignant cell clones [12]. To our knowledge, data on the risk of BC after prophylactic RT to the breast buds are scarce. Although a Swedish study demonstrated an increased risk of BC in PC patients diagnosed between 1958 and 1998, the risk was not associated with RT to the breast buds [13]. The authors concluded that the increased BC risk may be attributed to the estrogen treatment used at that time [13, 14]. Regarding BC risk after prophylactic RT, we have only identified three case reports; one patient with spindle cell carcinoma 8 years after RT, and two patients with phyllodes breast tumor 6 and 9 years after RT, respectively[15, 16, 17].

The aim of our study was to evaluate whether the risk of breast cancer in men with prostate cancer as their first cancer diagnosis was influenced by prophylactic radiotherapy to the breast buds in order to prevent antiandrogen induced gynecomastia.

Methods and Materials

Patients and data collection

To report new cancer cases to the Cancer Registry of Norway (NCR) has been mandatory by law since 1953, and since 1997 the NCR also has collected treatment data from all Norwegian radiotherapy units [10]. The quality of the registry is known to be good, with a completeness of 99 % and high validity [10, 18]. In our study we analyzed NCR data on all

patients diagnosed with PC as their first cancer diagnosis, between 1997 and 2014, with follow- up to December 31 2014. In all patients the date of birth, PC diagnosis and subsequent first BC if diagnosed (3 months or more following the diagnosis of PC) was recorded. Patients with a cancer diagnosis prior to their PC diagnosis were excluded to avoid a possible bias caused by RT before 1997. We registered data on all RT given (curative and palliative) after the PC diagnosis, including region of treatment, total dose in Gy and date of treatment start. In this study period, RT to the breast buds was given to Norwegian men on the sole indication to avoid gynecomastia caused by antiandrogen monotherapy. In patients who had received such prophylactic RT to the breast buds, the registration also included the number of fractions given. Morphological classification of tumors according to the International Classification of Disease for Oncology Third Edition (ICD-O-3) were collected for all BC cases [19]. Follow-up was from 3 months after PC diagnosis to the date of first BC diagnosis, death, emigration or December 31 2014, which ever occurred first.

Statistical analyses

Multivariable Fine and Gray competing risk regression, treating death as competing risk, was used to estimate subdistribution hazard ratio (SHR) and 95 % confidence interval for the risk of BC in PC patients treated with prophylactic RT to the breast buds as compared with non-irradiated PC patients [20]. In addition to prophylactic RT, the statistical model included age at diagnosis (categorized: 0-59, 60-69, 70-79 and 80+ years, respectively) and time of diagnosis categorized in periods (1997-2003, 2004-2009, 2010-2014). Ideally, the model would also include different fractionation regimes, but this was not possible due to a low number of BC cases. To avoid immortal time bias prophylactic RT was included as a time-varying covariate.

Standardized incidence ratio (SIR) with a 95 % CI was calculated by comparing the observed number of BC cases in the cohort to the expected number of BC cases derived from age- and calendar time-specific incidence rates in the comparable Norwegian male population. Estimates from the Aalen-Johansen estimator, taking into account the competing risk of death, was used to graphically illustrate the risk of breast cancer during follow-up [21]. P-values below 0.05 were considered statistically significant. All analyses were made using the software package STATA IC 14 (Stata Corp 2017).

Results

In the NCR, a total of 62 349 patients were registered with PC as their first cancer diagnosis in the period 1997-2014. Of these, 59 169 had positive follow up time and were eligible for analysis. The mean age at PC diagnosis was 70 years. A total of 7864 (13.3%) patients received prophylactic RT to the breast buds, with a total dose of 10- 15 Gy. Although the treatment was not strictly standardized, the typical electron energy used was 6 or 9 MeV and the field diameter was 7- 10 cm. The majority of the patients, n= 5035 (64 %), received 15 Gy to each breast bud in a single fraction (Table 1). Excluding prophylactic RT to the breast buds, RT was registered in 19 144 (32%) patients, including 4923 (62.6%) and 14 221 (27.7%) within the prophylactic breast bud RT and non- prophylactic breast bud RT groups, respectively (Table 2).

A total of 12 men were diagnosed with BC, including 9 cases of infiltrative ductal carcinoma, 2 cases of malignant phyllodes tumor, 1 case of mucinous adenocarcinoma and 1 case of Pagets disease. Of these 12 men, 3 had received prophylactic RT. The first of the 3 patients, born in 1927 and diagnosed with PC in 2007, received prophylactic RT in 2007 and was

diagnosed with phyllodes tumor in 2012. The histopathology report described a malignant phyllodes tumor in breast tissue with gynecomastia. The second patient born in 1949 was diagnosed with PC in 2007 and received prophylactic RT in 2008. He was diagnosed with phyllodes tumor in 2013. The histopathology report described a malignant phyllodes tumor and also fibroadenoma in breast tissue. The third patient born in 1944 was diagnosed with PC in 1998 and received prophylactic RT in 1999. He was diagnosed with bilateral infiltrative ductal carcinomas in 2014 [10]. The median time to BC for the nine men who were not treated with prophylactic RT was 4.8 years, range 0.8-9.1 years.

Median follow-up time was 6.8 and 3.6 years in the prophylactic RT and non-prophylactic RT groups, respectively (Table2). The standardized incidence ratio for BC was 0.996 95 % CI 0.57-1.75. The risk of BC was not statistically significantly different in patients given prophylactic RT as compared to the non-irradiated patients, SHR 1.62 95% CI 0.44-5.91 adjusted for age and time of diagnosis (Table 3). The actual risk for developing BC was estimated to approximately 0.2% for the irradiated patients and below 0.1 % for the non-irradiated patients (Figure 1).

Discussion

The main finding in this study was that radiotherapy to the breast buds in prostate cancer patients was not statistically significantly associated with increased or reduced risk of breast cancer. This is reassuring, since practically all Norwegian patients are offered prophylactic RT to the breast buds when prescribed antiandrogen monotherapy. However, the number of BC cases in our study was small, leading to a wide 95 % CI which does not preclude an increased risk. On the basis of our results and the fact that BC in men is a rare disease, we have no reason to assume that there is a clinically significant change in the risk of BC in men treated

with prophylactic RT. Three patients were diagnosed with BC after prophylactic RT to the breast buds. It is noteworthy that two of these three patients had malignant phyllodes breast tumors, both diagnosed about five years after RT. Phyllodes tumor (PT) has its origin both from epithelial and stromal cells of the breast, and is classified into benign, borderline or malignant subtypes. It is a very rare tumor that accounts for less than 1 % of all breast neoplasms in women, and in men only sporadic cases are reported [17, 22, 23]. Malignant PT behaves similar to sarcomas and may develop blood-borne metastases. The treatment is surgery. Malignant tumors have a tendency to recur locally, but the prognosis is generally favorable [23, 24, 25]. From 1953 -2015, 795 men were diagnosed with BC in Norway, and the majority were infiltrating ductal carcinomas. Interestingly, only two men found in our study were diagnosed with malignant PT in this period [10].

The three case reports we found in the literature reporting on male BC after radiotherapy to the breast buds, included two cases of PT 6 and 9 years after prophylactic RT prior to start of estradiol phosphate and bicalutamid, respectively. In addition, one case of high-grade spindle cell sarcoma was diagnosed 8 years after start of bicalutamid treatment and RT [15, 16, 17]. It is known that RT for BC is associated with a small increased risk of secondary cancers, typically affecting organs adjacent to the irradiated area as well as distant structures [26]. However, the treatment fields and radiation doses given in BC and PMRT differ considerably, and studies on secondary cancers after RT for BC are probably not relevant for prophylactic RT to the breast buds. In BC, patients typically receive 50 Gy in fractionated RT to the entire mammary gland, in contrast to the small fields and single fractions most commonly applied in prophylactic RT to the breast buds.

Gynecomastia is known to be associated with increased risk of PT of the breast. In a review on cystosarcoma phyllodes tumors in men reported by Konstantinakos et al., 7 of the 13 reported cases had gynecomastia [23]. More recent case reports also have identified gynecomastia as a risk factor for male PT [22, 27]. Similar to the three reported cases in the literature, one patient with PT in our study had gynecomastia, whereas the other had fibroadenoma of the breast, which is strongly associated to gynecomastia [28].

Prophylactic RT to the breast buds is not 100% effective. Fagerlund et al. reported some degree of gynecomastia in up to 50 % of men who had received RT [29]. Thus, it is possible that the two cases of phyllodes tumors in our study were caused by medication induced gynecomastia rather than the prophylactic irradiation.

In the present study, the mean age at PC diagnosis in men treated with prophylactic RT to the breast buds was 69 years. Currently, patients treated with radical prostatectomy are typically younger [30]. Many of these need salvage local radiotherapy, and there is evidence that a substantial proportion should be offered additional hormonal treatment [2]. Accordingly, it is possible that future patients, who will receive prophylactic RT to the breast buds at a relatively younger age, will be more susceptible to serious long term side effect such as BC.

Of the 59 169 patients in our study population, 19 144 (32.3%) received RT excluding prophylactic breast bud RT, most frequently to the prostatic and pelvic regions. Only 0.5 % of the patients treated with other RT than prophylactic RT were reported to receive RT to the thoracic region. Unfortunately, the region of RT was not registered in 8426 (44 %) of the 19 144 patients. We have, however, no reason to believe that a higher proportion of these patients had RT to the thoracic region than the patients with region of RT registered. None

of the BC patients received RT (other than prophylactic breast bud RT) to the thoracic region, and it seems unlikely that RT excluding prophylactic RT could have influenced our results to any substantial degree.

Prophylactic oral tamoxifen can be an alternative to prophylactic RT to avoid gynecomastia. In a review by Fagerlund et al., a daily dose of tamoxifen 20 mg was reported to be more effective than RT, with a low risk of minor side effects [29]. To our knowledge tamoxifen is not commonly prescribed in Norway for this indication, but may be considered in the future as an alternative to RT.

This study has some limitations. Secondary cancers are classically considered to be radiation induced if diagnosed after a latency period of 5 years or more after exposure to radiation [31]. In our study the median follow-up was 6.8 years in the irradiated group and 3.6 years in the non-irradiated group. Therefore, it is possible that with longer follow-up, the number of breast cancer cases in this population will increase. All the patients in our cohort had PC as their first cancer diagnosis, which means that patients with BC as first diagnosis were not included. One could suspect that this inclusion criterion would leave us with a cohort of patients less susceptible for BC. A comparison of BC incidence in our cohort with the expected incidence in a comparable standard male population gave a SIR of 0.996, indicating that this is merely a theoretical concern. The Li-Fraumeni syndrome, caused by a mutated "Tumor protein 53" (TP53) gene, is known to increase the risk of PT. Although the TP53 status was unknown, there is no particular reason to expect that the two patients with PT, who were diagnosed with PC at ages 80 and 67 years, carried this mutation. [32].Similarly, we do not have data on smoking habits. From clinical experience we know that smokers are less often offered radical treatment than non-smokers, and thus the proportion of smokers

may be higher in the prophylactic RT group. There is some increasing evidence that smoking may increase BC risk, and in theory smoking habits may confound our estimates [33]. Smoking is, however, not a known risk factor for PT of the breast, and although the possibility cannot be excluded, smoking does not seem to play an important confounding role in our analyses. Another limitation is that we do not have information on the genetic profile of our patients. Mutations in breast cancer gene (BRCA) 1 and 2 are known risk factors for BC and PC [34, 35]. The extent of BRCA mutations in the Norwegian population is small and we know that about 2 % of female BC is caused by BRCA mutations [36]. The extent of BRCA mutations in Norwegian PC and male BC is unknown, but we have no reason to believe that these mutations are major causes of the diseases.

Conclusion

In this registry based study, we did not find that the risk of breast cancer was influenced by prophylactic radiotherapy to the breast buds in men with PC. Accordingly, although cancer is a feared late side effect of ionizing radiation the results of the present study do not give reason to warn against prophylactic breast bud RT. As in the general male population, BC was rare (n=3) among patents given prophylactic RT. It is, however, noteworthy that 2 of these were malignant phyllodes tumors, an extremely rare type of breast cancer. The incidence of breast cancer can be expected to rise with additional follow-up. It is therefore possible that subsequent analyses of this study population may alter the main conclusion.

References

[1] Widmark A, Klepp O, Solberg A, et al. Endocrine treatment, with or without radiotherapy, in locally advanced prostate cancer (SPCG-7/SFUO-3): an open randomised phase III trial. Lancet (London, England). 2009 Jan 24;373(9660):301-8.

[2] Shipley WU, Seiferheld W, Lukka HR, et al. Radiation with or without Antiandrogen Therapy in Recurrent Prostate Cancer. The New England journal of medicine. 2017 Feb 02;376(5):417-428.

[3] Thomsen FB, Brasso K, Christensen IJ, et al. Survival benefit of early androgen receptor inhibitor therapy in locally advanced prostate cancer: long-term follow-up of the SPCG-6 study. European journal of cancer (Oxford, England : 1990). 2015 Jul;51(10):1283-92.

[4] Tyrrell CJ, Payne H, Tammela TL, et al. Prophylactic breast irradiation with a single dose of electron beam radiotherapy (10 Gy) significantly reduces the incidence of bicalutamide-induced gynecomastia. International journal of radiation oncology, biology, physics. 2004 Oct 01;60(2):476-83.

[5] Widmark A, Fossa SD, Lundmo P, et al. Does prophylactic breast irradiation prevent antiandrogen-induced gynecomastia? Evaluation of 253 patients in the randomized Scandinavian trial SPCG-7/SFUO-3. Urology. 2003 Jan;61(1):145-51.

[6] Ozen H, Akyol F, Toktas G, et al. Is prophylactic breast radiotherapy necessary in all patients with prostate cancer and gynecomastia and/or breast pain? The Journal of urology. 2010 Aug;184(2):519-24.

[7] Iversen P, Johansson JE, Lodding P, et al. Bicalutamide 150 mg in addition to standard care for patients with early non-metastatic prostate cancer: updated results from the Scandinavian Prostate Cancer Period Group-6 Study after a median follow-up period of 7.1 years. Scandinavian journal of urology and nephrology. 2006;40(6):441-52.

[8] NICE. Prostate cancer: diagnosis and management [Internet]. 2014 [cited 2017 June 22]. Available from: https://www.nice.org.uk/Guidance/CG175

[9] Wirth MP, See WA, McLeod DG, et al. Bicalutamide 150 mg in addition to standard care in patients with localized or locally advanced prostate cancer: results from the second analysis of the early prostate cancer program at median followup of 5.4 years. The Journal of urology. 2004 Nov;172(5 Pt 1):1865-70.

[10] The Cancer Registry of Norway. Available from: https://www.kreftregisteret.no/en.

[11] Helsedirektoratet. Nasjonalt handlingsprogram med retningslinjer for diagnostikk, behandling og oppfølging av prostatakreft [Internet]. 2015 [cited 2017 May 30]. Available from: http://www.helsebiblioteket.no/retningslinjer/prostatakreft

[12] Kumar S. Second malignant neoplasms following radiotherapy. International journal of environmental research and public health. 2012 Dec 18;9(12):4744-59.

[13] Thellenberg C, Malmer B, Tavelin B, et al. Second primary cancers in men with prostate cancer: an increased risk of male breast cancer. The Journal of urology. 2003 Apr;169(4):1345-8.

[14] Karlsson CT, Malmer B, Wiklund F, et al. Breast cancer as a second primary in patients with prostate cancer--estrogen treatment or association with family history of cancer? The Journal of urology. 2006 Aug;176(2):538-43.

[15] Lewis R, Cassoni A, Payne H. Prophylactic breast bud radiotherapy for patients taking bicalutamide: should this still be practised for patients with prostate cancer? Case reports in oncological medicine. 2012;2012:239269.

[16] Johansson L, Balldin G. Malignant cystosarcoma phyllodes in a man treated with polyestradiolphosphate. Case report. Acta chirurgica Scandinavica. 1986 Dec;152:781-5.

[17] Karihtala P, Rissanen T, Tuominen H. Male Malignant Phyllodes Breast Tumor After Prophylactic Breast Radiotherapy and Bicalutamide Treatment: A Case Report. Anticancer research. 2016 Jul;36(7):3433-6.
[18] Larsen IK, Smastuen M, Johannesen TB, et al. Data quality at the Cancer Registry of Norway: an overview of comparability, completeness, validity and timeliness. European journal of cancer (Oxford, England : 1990). 2009 May;45(7):1218-31.
[19] International classification of Desease for Oncology ICD-O-3 online [Internet]. WHO. 2013. Available from: http://codes.iarc.fr/.
[20] Fine JP, Gray RJ. A Proportional Hazards Model for the Subdistribution of a Competing Risk. Journal of the American Statistical Association. 1999;94(446):496-509.
[21] Aalen OO, Johansen S, xf, et al. An Empirical Transition Matrix for Non-Homogeneous Markov Chains Based on Censored Observations. Scandinavian Journal of Statistics. 1978;5(3):141-150.
[22] Kim JG, Kim SY, Jung HY, et al. Extremely rare borderline phyllodes tumor in the male breast: a case report. Clinical imaging. 2015 Nov-Dec;39(6):1108-11.
[23] Konstantakos AK, Graham DJ. Cystosarcoma phyllodes tumors in men. The American surgeon. 2003 Sep;69(9):808-11.
[24] Campagnaro EL, Woodside KJ, Xiao SY, et al. Cystosarcoma phyllodes (phyllodes tumor) of the male breast. Surgery. 2003 Jun;133(6):689-91.
[25] Tan BY, Acs G, Apple SK, et al. Phyllodes tumours of the breast: a consensus review. Histopathology. 2016 Jan;68(1):5-21.
[26] Grantzau T, Overgaard J. Risk of second non-breast cancer among patients treated with and without postoperative radiotherapy for primary breast cancer: A systematic review and meta-analysis of population-based studies including 522,739 patients. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2016 Dec;121(3):402-413.
[27] Chougule A, Bal A, Rastogi P, et al. Recurrent phyllodes tumor in the male breast in a background of gynaecomastia. Breast disease. 2015;35(2):139-42.
[28] Agarwal P, Kohli G. Fibroadenoma in the male breast: Truth or Myth? Turkish Journal of Surgery/Ulusal cerrahi dergisi. 2016;32(3):208-11.
[29] Fagerlund A, Cormio L, Palangi L, et al. Gynecomastia in Patients with Prostate Cancer: A Systematic Review. PloS one. 2015;10(8):e0136094.
[30] Hamdy FC, Donovan JL, Lane JA, et al. 10-Year Outcomes after Monitoring, Surgery, or Radiotherapy for Localized Prostate Cancer. The New England journal of medicine. 2016 Oct 13;375(15):1415-1424.
[31] Murray L, Henry A, Hoskin P, et al. Second primary cancers after radiation for prostate cancer: a systematic review of the clinical data and impact of treatment technique. Radiotherapy and oncology : journal of the European Society for Therapeutic Radiology and Oncology. 2014 Feb;110(2):213-28.
[32] Ossa CA, Molina G, Cock-Rada AM. Li-Fraumeni syndrome. Biomedica : revista del Instituto Nacional de Salud. 2016 Jun 03;36(2):182-7.
[33] Andersen ZJ, Jorgensen JT, Gron R, et al. Active smoking and risk of breast cancer in a Danish nurse cohort study. BMC cancer. 2017 Aug 22;17(1):556.
[34] Onami S, Ozaki M, Mortimer JE, et al. Male breast cancer: an update in diagnosis, treatment and molecular profiling. Maturitas. 2010 Apr;65(4):308-14.
[35] Bancroft EK, Page EC, Castro E, et al. Targeted prostate cancer screening in BRCA1 and BRCA2 mutation carriers: results from the initial screening round of the IMPACT study. European urology. 2014 Sep;66(3):489-99.
[36] Moller P, Hagen AI, Apold J, et al. Genetic epidemiology of BRCA mutations--family history detects less than 50% of the mutation carriers. European journal of cancer (Oxford, England : 1990). 2007 Jul;43(11):1713-7.

Disclosure: The study used data from the Cancer Registry of Norway. The interpretation and reporting of these data are the sole responsibility of the authors, and no endorsement by the Cancer Registry of Norway is intended nor should be inferred.

Table 1. Distribution of different fractionation regimens in 7864 men who received prophylactic breast bud radiation therapy.

Fractionation (Gy)	Total dose (Gy)	Number of patients Total 7864
15 Gy x1	15	5035 (64.0%)
12 Gy x1	12	1289 (16.4%)
4 Gy x3	12	1027 (13.1%)
10 Gy x1	10	505 (6.4%)
other	other	5 (0.1%)

Data in parenthesis are percentages.

Table 2. Patient, tumor and treatment characteristics.

	PRT patients	Non-PRT patients	Total
No. of patients	7 864 (13.3%)	51 305 (86.7%)	59 169(100%)
No. of BC patients	3	9	12
Year of diagnosis			
1997-2003	2586(32.9%)	15 360(29.9%)	17 946(30.3%)
2004-2009	3554(45.2%)	17 927(34.9%)	21 481(36.3%)
2010-2014	1724(21.9%)	18 018(35.1%)	19 742(33.4%)
Stage, PC diagnosis			
Localized	3593(45.7%)	26 851(52.3%)	30 444(51.5%)
Regional met.	1852(23.6%)	6883(13.6%)	8735(14.8%)
Distant met.	246(3.1%)	5455(10.6%)	5701(9.6%)
Unknown	2173(27.6%)	12 116(23.6%)	14 289(24.2%)
Age, mean, PC diagnosis, y (range)	69 (42,94)	70 (37,101)	70 (37,101)
Follow-up, median, y(range)	6.8 (0.04, 18.2)	3.6 (0.002, 18.4)	4 (0.002, 18.4)
Follow up, person-y	46 266	266 613	312 879
Age, mean, PRT, y (range)	70 (44,95)	-	-
Other RT	4923(62.6%)	14 221(27.7%)	19 144
No other RT	2941(37.4%)	37 084(72.3%)	40 025

Abbreviations: PC=prostate cancer; PRT= prophylactic radiotherapy to the breast buds; BC= breast cancer; Other RT= all radiotherapy given to the patient excluding PRT.

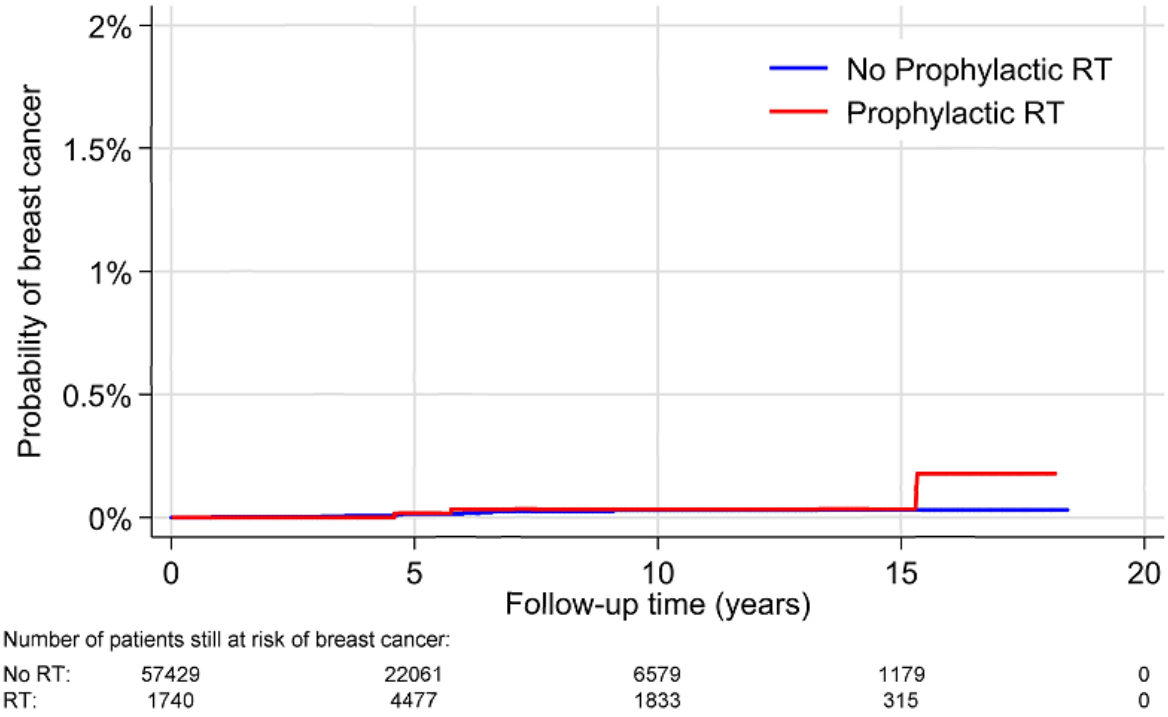
Data in parenthesis are percentages.

Table 3. Univariate and multivariate analysis for the risk of breast cancer.

	SHR	p-value	95 % CI
Univariate analysis			
PRT Yes vs no	2.02	0.288	0.55-7.35
Multivariate analysis			
PRT Yes vs no	1.62	0.465	0.44-5.91
Age at diagnosis, y : 0-59	1		
60-69	1.10	0.907	0.22-5.51
70-79	0.73	0.715	0.13-4.06
80+	<0.01	NA	NA
Time of diagnosis: 1997-2003	1		
2004-2009	1.01	0.992	0.31-3.29
2010-2014	<0.01	NA	NA

Abbreviations: SHR= Subdistribution hazard ratio, CI=Confidence interval, PRT=Prophylactic radiotherapy to the breast buds, NA= Not applicable

Fig. 1. Risk of breast cancer stratified by follow-up time in men with prostate cancer.



Abbreviation: RT= radiation therapy (to the breast buds).