SHORT COMMUNICATION

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A population-based analysis of secondary malignancies in breast cancer patients receiving breast reconstruction

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Background: There is an ongoing debate about the relationship between breast implants and secondary malignancies.

Methods: Breast cancer patients undergoing surgical reconstruction after mastectomy by either implants or autologous flap were identified in the Surveillance, Epidemiology and End Results registry between 1998 and 2002. The occurrence of secondary malignancies at least 1 year after diagnosis was compared between breast reconstruction with implants *vs* autologous flap.

Results: Of 7955 women, 3727 underwent reconstruction using implants and 4228 using autologous flap. The incidence of secondary tumours was similar in both the groups (hazards ratio (HR) = 1.02, 95% confidence interval (CI): 0.82–1.26, $P = 0.880$). For lung cancer, a significantly increased risk for implants (HR = 2.51, 95% CI: 1.28–4.95, $P = 0.005$) was observed.

Conclusions: Except for lung cancer, no association between implants and secondary malignancies including lymphomas was observed.

Surgical breast reconstruction is an important option to improve the quality of life in women undergoing mastectomy for breast cancer. Options for breast reconstruction include tissue expander/implants or autologous reconstruction using tissue flaps. Tissue expander/implant reconstruction is the most commonly practiced alloplastic reconstructive procedure in the United States (Alderman *et al*, 2011) and is used as an alternative to autologous reconstruction (Lin *et al*, 2001; Chawla *et al*, 2002). Breast implants are associated with a slightly higher risk of reconstructive failure or surgical-site infection as compared with autologous reconstruction, but with lower rates of skin or flap necrosis (Tsoi *et al*, 2014). Recently, anaplastic large-cell lymphoma (ALCL) has been associated with reconstructive breast implants following breast cancer (Duvic *et al*, 1995; Keech and Creech, 1997; Agarwal *et al*, 2010; Jewell *et al*, 2011; Taylor *et al*, 2013), resulting in a white paper issued by the US Food and Drug Administration in 2011, based on 34 cases of breast implant-associated ALCL in an estimated 5–10 million women with breast implants (Center for Devices and Radiological Health, 2011). We assessed the potential association between secondary malignancies and the type of breast reconstruction in a large, unselected group of breast cancer patients by applying stratified propensity score matching to correct for potential case selection bias.

MATERIALS AND METHODS

Database and cohort definition. The 2014 submission of the Surveillance, Epidemiology and End Results (SEER) program was

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used as data source. From 262 445 female breast cancer patients diagnosed between 1998 and 2002, 8044 were eligible for the analysis after exclusion of patients with *in situ* carcinoma ($N=47\,121$), lacking diagnosis by histology ($N=4960$), secondary malignancies prior to breast cancer ($N=31\,489$), other histology than adenocarcinoma, cystic, mucinous, serous, ductal, lobular or mixed ductal and lobular carcinoma ($N=4748$), other than stage I–III ($N=18\,358$), pre- or intraoperative radiation ($N=1183$), lacking income data on the county level ($N=1606$), no subcutaneous, simple, radical or modified radical mastectomy ($N=86\,317$), no reconstruction ($N=58\,619$) and follow-up of <1 year ($N=89$). The remaining 7955 patients were grouped according to whether they had received breast reconstruction by autologous flaps or by implants.

Statistical analysis. Statistical analysis was performed using the R statistical software (www.r-project.org). After descriptive analysis, logistic regression was performed to assess the association between patient and treatment characteristics. Potential confounders were tumour stage, histology, grading, ER and PR status, type of mastectomy, local radiotherapy, year of initial diagnosis, patient age, ethnicity, marital status and census tract level of household income. Secondary malignancies were treated as time-to-event-data and counted only if they occurred at least 1 year after breast cancer diagnosis. Only the first case of breast cancer was considered to avoid the inclusion of relapses in the analysis. Secondary malignancies were grouped according to the Collaborative Stage scheme. The association between breast reconstruction and patient characteristics was analysed by multivariable logistic regression. The association between secondary malignancies and breast reconstruction by autologous flap *vs* implants was assessed by Cox regression stratified for age and by propensity score matching using the 'MatchIt' and 'optmatch' R packages (Ho *et al*, 2007). Based on the results of the matching procedure, a second Cox regression analysis was performed. Both stratified and propensity score-matched Cox regression was repeated for each entity of secondary malignancies. Finally, we assessed potential differences in smoking-related causes of death between the two study groups using Cox regression analysis.

RESULTS

Patient characteristics. No significant trend in the annual rate of breast reconstruction on all mastectomies was found with rates of 11.0, 12.6, 12.3, 12.0 and 12.1% from 1998 to 2002 ($P_{Trend}=0.233$). Of the 7955 women included in the study, 3727 (46.9%) received breast reconstruction using implants and 4228 (53.1%) received breast reconstruction using an autologous flap (Table 1). The median follow-up was 10.3 years (Interquartilerange: 9.2–11.6 years).

Secondary malignancies. A total of 874 secondary malignancies were encountered. Of these, 514 secondary breast carcinomas and 29 malignancies occurring within 1 year after breast cancer diagnosis were excluded. The 340 secondary malignancies in the analysis were distributed as follows: Lung carcinoma ($N=40$, 0.5%), colorectal cancer ($N=38$, 0.5%), endometrial cancer ($N=32$, 0.4%), melanoma ($N=31$, 0.4%), thyroid cancer ($N=30$, 0.4%), ovarian cancer ($N=28$, 0.4%), kidney cancer ($N=25$, 0.3%), lymphoma ($N=21$, 0.3%), haematological malignancies ($N=21$, 0.3%), bladder cancer ($N=13$, 0.2%), pancreatic cancer ($N=12$, 0.2%), anal cancer ($N=8$, 0.1%), neuroendocrine tumours ($N=6$, 0.1%), brain cancer ($N=5$, 0.1%), cancer of cervix uteri ($N=5$, 0.1%), peritoneal cancer ($N=5$, 0.1%), soft tissue sarcoma ($N=5$, 0.1%), hepatobiliary cancer ($N=3$), appendiceal cancer ($N=2$), oesophageal cancer ($N=2$), myeloma ($N=2$), parotideal cancer ($N=2$), bone cancer ($N=1$), skin cancer other than melanoma ($N=1$), small intestinal cancer ($N=1$) and cancer of the vulva ($N=1$).

Association between the type of breast reconstruction and secondary malignancies. In the flap and implant group, 176 (4.2%) and 164 (4.4%) secondary malignancies were encountered, respectively (hazards ratio (HR) = 1.02, 95% confidence interval (CI): 0.82 − 1.26, $P=0.880$ in stratified Cox regression). Figure 1 depicts the cumulative incidence of secondary malignancies for both groups. The HR for breast reconstruction using an implant *vs* autologous flap for secondary malignancies occurring at least 1 year after diagnosis of breast cancer is outlined in Figure 2. There was no significant association between secondary tumours and breast reconstruction by implants except for lung carcinoma, and this association was substantial when stratified for age (HR = 2.51, 95% CI: 1.28–4.96, $P=0.005$) and when propensity matched (HR = 3.22, 95% CI: 1.44–7.20, $P=0.002$). No significant differences between groups were found for any secondary malignancy including lymphomas ($P=0.657$ in age-stratified Cox regression). The following lymphoma entities were encountered in the implant group: unspecified lymphoma ($N=1$), diffuse, large B-cell lymphoma ($N=5$), follicular lymphoma grade 3 ($N=1$), cutaneous T-cell lymphoma ($N=1$), primary cutaneous anaplastic large-cell lymphoma ($N=1$). The following lymphoma were encountered in the flap group: unspecified lymphoma ($N=2$), Hodgkin lymphoma with nodular sclerosis ($N=1$), diffuse, large B-cell lymphoma ($N=3$), follicular lymphoma grade 2 ($N=1$), marginal zone B-cell lymphoma ($N=4$), follicular lymphoma grade 3 ($N=1$). Combined cardiovascular and pulmonary deaths, including COPD, were significantly more frequent in the implant compared with the flap group (2.3% *vs* 1.3%, $P=0.001$). These results were partly confirmed in a sensitivity analysis including 2475 patients with *in situ* carcinoma of the breast: Overall risk for secondary malignancies after reconstructive breast implants was similar with reconstructive breast implants *vs* autologous flap (HR = 0.96, 95% CI: 0.79 − 1.16, $P=0.665$), although there was a numerically increased risk of lung cancer after reconstructive breast implants *vs* autologous flap using age-stratified Cox regression (HR = 1.69, 95% CI:0.97–2.95, $P=0.061$) or by using propensity score-adjusted Cox regression (HR = 1.78, 95% CI:0.96–3.33, $P=0.065$).

DISCUSSION

We found a significant association between lung cancer and reconstructive breast implants as compared with autologous flap, both by age-stratified Cox regression analysis and propensity score matching. However, we did not find any association between the occurrence of lymphoma and reconstructive breast implants, as previously suggested (Duvic *et al*, 1995; Keech and Creech, 1997; Center for Devices and Radiological Health, 2011; Jewell *et al*, 2011; Taylor *et al*, 2013; Kellogg *et al*, 2014; Laurent *et al*, 2016). The average time between first implant placement and the occurrence of breast implant-associated lymphoma was 13.3 years (Locke and Lofts, 2015), moderately longer than the median follow-up time in the present study. To our knowledge, the correlation between lung cancer and breast reconstruction by implants has not been described so far. In the past, numerous epidemiological studies examined the association between cosmetic breast implants and the incidence of cancer (Malone *et al*, 1992; Bryant and Brasher, 1995; Deapen *et al*, 1997; Kern *et al*, 1997; McLaughlin *et al*, 1998; Brinton *et al*, 2000; Brinton *et al*, 2001; Pukkala *et al*, 2002; Breiting *et al*, 2004; Friis *et al*, 2006), and breast silicone implants were declared not to be carcinogenic (Bondurant *et al*, 1999). Since 2006, however, four retrospective studies have suggested an increased risk of lung cancer among women with

Table 1. Patient characteristics and bias for type of reconstruction

	Patient characteristics				Logistic regression for prediction of implant[a]	
	Total $N=7955$	Implant group $N=3727$	Flap group $N=4228$	P-value[b]	Odds ratio (95% confidence interval)	P-value[c]
Stage (AJCC 6th edition)						
I	3201 (40.2%)	1604 (43.0%)	1597 (37.8%)	<0.001	Reference	<0.001
IIA	2193 (27.6%)	1067 (28.6%)	1126 (26.6%)		0.96 (0.86–1.07)	
IIB	1145 (14.4%)	474 (12.7%)	671 (15.9%)		0.73 (0.63–0.85)	
IIIA	905 (11.4%)	395 (10.6%)	510 (12.1%)		0.80 (0.67–0.95)	
IIIB	122 (1.5%)	40 (1.1%)	82 (1.9%)		0.50 (0.33–0.74)	
IIIC	389 (4.9%)	147 (3.9%)	242 (5.7%)		0.63 (0.49–0.79)	
Histology						
Duktal/lobular malignoma	7674 (96.5%)	3598 (96.5%)	4076 (96.4%)	0.747	Reference	0.158
Other	281 (3.5%)	129 (3.5%)	152 (3.6%)		0.84 (0.65–1.07)	
Grading						
G1	1109 (13.9%)	571 (15.3%)	538 (12.7%)	<0.001	Reference	0.220
G2	3098 (38.9%)	1466 (39.3%)	1632 (38.6%)		0.88 (0.77–1.02)	
G3/4	3080 (38.7%)	1368 (36.7%)	1712 (40.5%)		0.85 (0.73–0.99)	
GX	668 (8.4%)	322 (8.6%)	346 (8.2%)		0.92 (0.76–1.12)	
ER status						
Positive	5230 (65.7%)	2520 (67.6%)	2710 (64.1%)	0.002	Reference	0.140
Negative	1532 (19.3%)	662 (17.8%)	870 (20.6%)		0.91 (0.78–1.07)	
Unknown/borderline	1193 (15.0%)	545 (14.6%)	648 (15.3%)		0.77 (0.57–1.04)	
PR status						
Positive	4462 (56.1%)	2148 (57.6%)	2314 (54.7%)	0.015	Reference	0.380
Negative	2147 (27.0%)	952 (25.5%)	1195 (28.3%)		0.97 (0.84–1.11)	
Unknown/borderline	1346 (16.9%)	627 (16.8%)	719 (17.0%)		1.20 (0.90–1.60)	
Mastectomy						
Modified radical	6035 (75.9%)	2795 (75.0%)	3240 (76.6%)	0.088	Reference	0.951
Other	1920 (24.1%)	932 (25.0%)	988 (23.4%)		1.00 (0.90–1.12)	
Radiation						
No Radiation	6435 (80.9%)	3073 (82.5%)	3362 (79.5%)	0.001	Reference	0.830
Postoperative radiation	1520 (19.1%)	654 (17.5%)	866 (20.5%)		0.99 (0.86–1.13)	
Year						
1998	859 (10.8%)	376 (10.1%)	483 (11.4%)	0.003	Reference	0.004
1999	992 (12.5%)	430 (11.5%)	562 (13.3%)		0.99 (0.82–1.19)	
2000	2066 (26.0%)	965 (25.9%)	1101 (26.0%)		1.12 (0.95–1.32)	
2001	2068 (26.0%)	1034 (27.7%)	1034 (24.5%)		1.28 (1.09–1.51)	
2002	1970 (24.8%)	922 (24.7%)	1048 (24.8%)		1.12 (0.95–1.33)	
Age (years)						
<35	405 (5.1%)	207 (5.6%)	198 (4.7%)	<0.001	Reference	<0.001
35–39	749 (9.4%)	340 (9.1%)	409 (9.7%)		0.76 (0.59–0.97)	
40–44	1260 (15.8%)	584 (15.7%)	676 (16.0%)		0.74 (0.59–0.93)	
45–49	1618 (20.3%)	756 (20.3%)	862 (20.4%)		0.75 (0.60–0.94)	
50–54	1480 (18.6%)	644 (17.3%)	836 (19.8%)		0.64 (0.51–0.80)	
55–59	1024 (12.9%)	448 (12.0%)	576 (13.6%)		0.63 (0.50–0.80)	
60–64	631 (7.9%)	329 (8.8%)	302 (7.1%)		0.88 (0.68–1.14)	
65–69	406 (5.1%)	201 (5.4%)	205 (4.8%)		0.84 (0.63–1.11)	
70+	382 (4.8%)	218 (5.8%)	164 (3.9%)		1.13 (0.84–1.50)	
Ethnicity						
Caucasian	6863 (86.3%)	3313 (88.9%)	3550 (84.0%)	<0.001	Reference	<0.001
African–American	686 (8.6%)	223 (6.0%)	463 (11.0%)		0.55 (0.47–0.66)	
Other/unknown	406 (5.1%)	191 (5.1%)	215 (5.1%)		0.95 (0.77–1.16)	
Marital status						
Married	5387 (67.7%)	2527 (67.8%)	2860 (67.6%)	0.155	Reference	0.070
Single/widowed	1415 (17.8%)	637 (17.1%)	778 (18.4%)		0.96 (0.85–1.08)	
Other/unknown	1153 (14.5%)	563 (15.1%)	590 (14.0%)		1.14 (1.00–1.30)	
Household income (census tract), $						
<$44 000	2649 (33.3%)	1224 (32.8%)	1425 (33.7%)	<0.001	Reference	<0.001
$44 000–$53 000	2459 (30.9%)	1084 (29.1%)	1375 (32.5%)		0.89 (0.79–0.99)	
$53 001–$62 000	1444 (18.2%)	686 (18.4%)	758 (17.9%)		1.00 (0.88–1.14)	
$62 001+	1403 (17.6%)	733 (19.7%)	670 (15.8%)		1.22 (1.07–1.40)	

Abbreviations: AJCC = American Joint Committee on Cancer; ER = estrogen receptor; PR = progesterone receptor.
[a]Likelihood ratio test.
[b]χ^2-test.
[c]Full model logistic regression for prediction of reconstruction with implant.

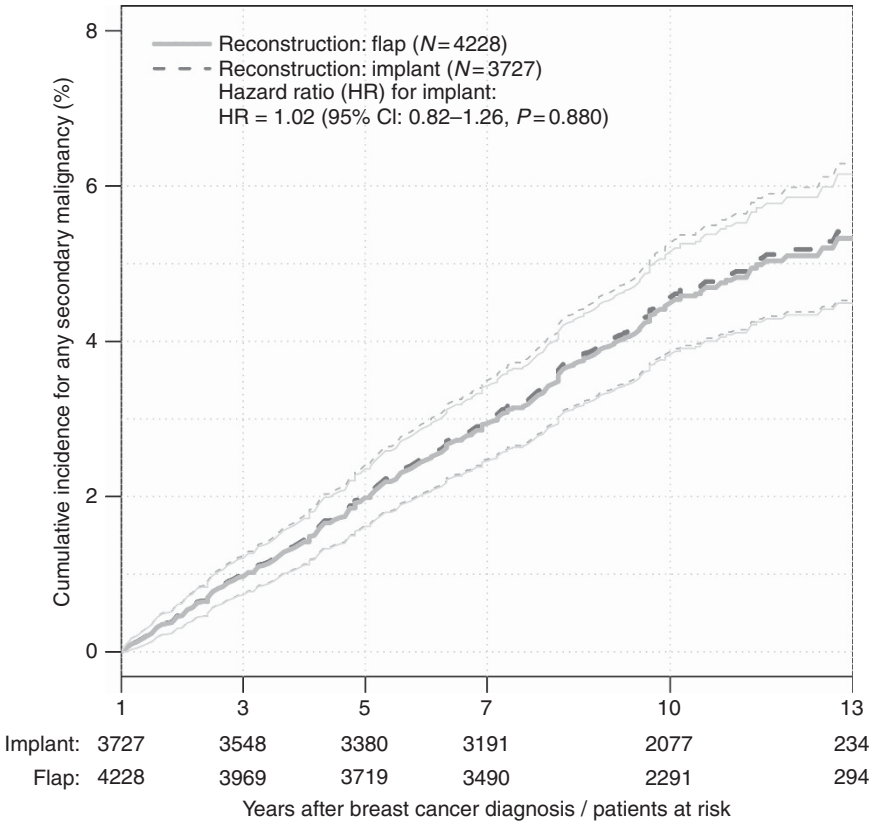

Figure 1. Cumulative incidence for secondary malignancies.

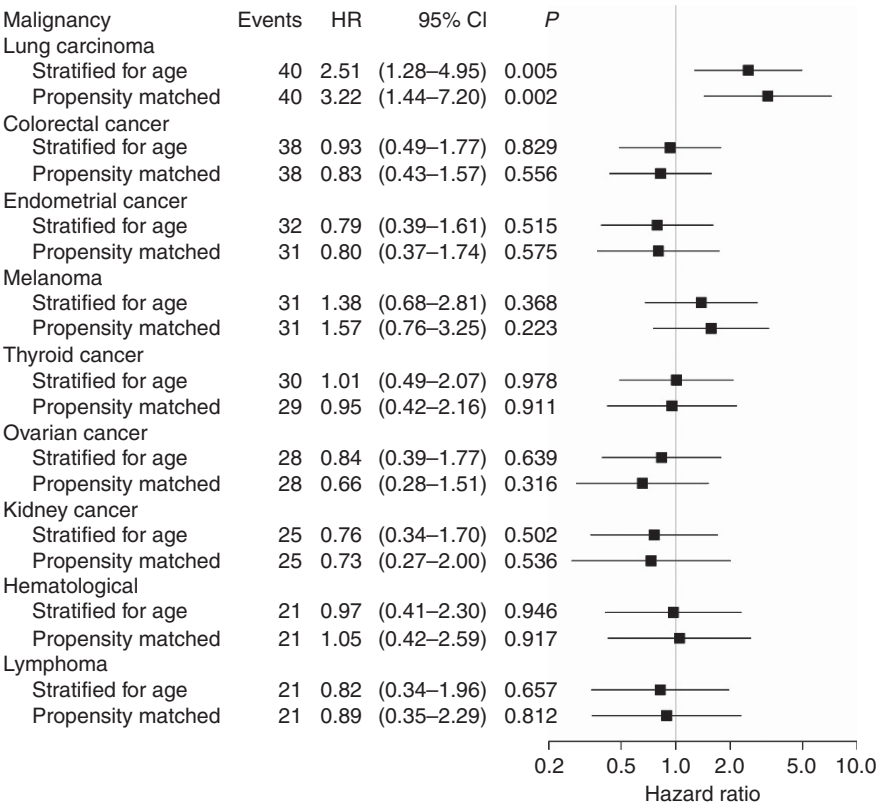

Figure 2. Risk for the nine most frequent secondary malignancies after reconstruction with implant compared to flap.

cosmetic breast implants, with standardised incidence ratios between 1.6 and 2.2 (McLaughlin *et al*, 2006; Deapen *et al*, 2007; Lipworth *et al*, 2007; Lipworth *et al*, 2009). The increased lung cancer risk in these women was suggested to be related to the higher prevalence of smoking in women with breast implants, but the present data do not allow to confirm such correlations.

The present study has several limitations, including a potential bias due to imbalances between the two study groups despite multivariable analysis and propensity score matching, the presence of unidentified prognostic factors and the fact that the SEER registry does not provide data on cardiovascular risk factors, which may have impacted on the decision to perform autologous flap reconstruction compared with breast implants. In conclusion, the present study shows an increased lung cancer risk in women receiving surgical reconstruction following mastectomy for breast cancer by implants as compared with autologous flaps. At the same time, breast reconstruction by implants is not associated with an increased risk of secondary lymphomas.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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