Connective Tissue Disease and Other Rheumatic Conditions Following Cosmetic Breast Implantation in Denmark

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Objective: To examine the occurrence of connective tissue diseases (CTDs) as well as ill-defined and other rheumatic conditions among Danish women with cosmetic silicone breast implants.

Patients and Methods: A total of 2761 women with breast implants and 8807 control subjects were identified from plastic surgery private clinics and from public hospital plastic surgery departments. Women operated on at plastic surgery private clinics were identified through the files of each clinic, while women operated on at public hospitals were identified using the nationwide Danish National Registry of Patients. The control group consisted of women who underwent cosmetic surgery other than breast implantation or who only had a consultation. All women were followed up from January 1, 1977, through December 31, 1996, through the Danish National Registry of Patients for the occurrence of CTD as well as ill-defined and other rheumatic conditions. For the study period January 1, 1977, through December 31, 1994, the Danish National Registry of Patients contains information on hospitalization only, whereas data on outpatient visits are included from 1995 on, thus improving the sensitivity of the data. The implant and control groups were compared with the Danish population rates for CTD and ill-defined and other rheumatic conditions, and a direct comparison between the implant and control groups was also performed.

Results: When compared with rates from the general population, no excess of definite CTD was observed in the implant cohorts. For ill-defined and other rheumatic conditions, statistically significant excesses of unspecified rheumatism were observed in both the implant and control cohorts when compared with national rates. A direct comparison between the implant and control cohorts found no material differences between the groups.

Conclusions: The findings of this study support previous investigations and independent review panel conclusions that an association between silicone breast implants and definite CTDs is unlikely. The observation of an excess of unspecified rheumatism among women with implants and among control women suggests that women undergoing cosmetic plastic surgery have hospitalization rates for this condition in excess of those from the general population.

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SILICONE BREAST implants were introduced in the early 1960s, following decades of breast augmentation using paraffin and silicone oil injections, autologous tissue, and polyvinyl sponge implants.1 The use of these techniques was greatly limited by adverse outcomes and numerous local complications.1 Compared with these methods, silicone implants had the advantage of significantly better outcomes, although the risk of local complications, such as capsular contraction, was not eliminated.23

It was not until the 1970s that the adverse systemic effects of silicone breast implants were considered. The placement of silicone implants adjacent to the breast tissue raised concern about the carcinogenic potential of breast implants. However, subsequent epidemiological studies have not identified an association between silicone breast implants and breast cancer or cancer at other sites.4-8

In the early 1980s case reports emerged suggesting an association between silicone breast implants and various connective tissue diseases (CTDs), in particular systemic sclerosis.9-21 Only limited analytic epidemiological data addressing this hypothesis were available22 then. As a consequence, in 1992, the Food and Drug Administration banned the use of silicone breast implants in the United States other than for reconstructive purposes or as part of prospective safety studies.22 Since then, many epidemiological studies addressing the potential association...
PATIENTS, MATERIALS, AND METHODS

Breast implantations have been performed at approximately 27 plastic surgery private clinics in Denmark. Each identified clinic was approached regarding participation in this study. Eight clinics, including 3 of the 4 largest, agreed to participate. From their files, we identified all women who had received breast implants from January 1, 1973, through December 31, 1995. For each woman, the following information was extracted: personal number of registration (PNR), date of implantation, type of implant (silicone gel filled single or double lumen, saline or other type of filler material), indication for implant surgery (cosmetic, reconstructive, asymmetry, revision, or other) and prior implantations, if any. The PNR is a unique 10-digit number that incorporates the date of birth and sex of all individuals in Denmark and secures unambiguous linkage between registers.

A total of 1955 women with breast implants were identified at the private clinics. Of these, 302 were excluded owing to the following reasons: invalid PNR, 19 (1%); foreign residency, 170 (9%); missing information on date of implantation, 2 (0.1%); reconstruction after breast cancer, 76 (4%); and older than 55 years at implantation, 35 (2%), leaving 1653 women in the private clinic implant cohort for follow-up (Table 1). Age restriction was applied to facilitate the age match with women in the comparison cohort described below. The large majority (91%) of women had had no prior implantation. Information on the validity of the PNR and residency was obtained from the Central Population Register, Copenhagen.

For each woman undergoing breast implant surgery, another woman undergoing other types of cosmetic treatment (including consultation only) was selected from the clinic files and whenever possible matched by age (±3 years) and calendar year (±18 months) at procedure or consultation, thus establishing a comparison group. Matching by age was impossible at one of the clinics. The variables extracted for women in the comparison group included PNR and date and type of treatment. The comparison group thus identified consisted of 2428 women. Exclusions from this group were made owing to invalid PNR, 52 (2%); foreign residency, 178 (7%); missing information on date or type of treatment, 38 (2%); matched implantee had undergone reconstruction after breast cancer, 59 (2%); older than 55 years at procedure or consultation, 282 (12%); and overlap with the implantation group, 83 (3%), leaving 1736 women in the private clinic comparison cohort for follow-up (Table 1). The most frequent treatments in the comparison cohort were breast surgery other than implantation (breast reduction and mastopexia) (24%), facial surgery (21%), skin excisions (21%), and abdominal surgery (13%). Eighteen percent of the women in the comparison cohort had only an initial consultation for cosmetic surgery at the clinic.

A second implant cohort was identified through the NRP. This cohort comprises women who underwent cosmetic breast implant surgery at Danish public hospitals during the period January 1, 1977, through December 31, 1992. The identification of this cohort of 1135 women is described in detail elsewhere. Duplicate registries in both the private and public implant cohorts were found for 27 of the 1135 women; in the individual cohort analyses, these women were included in both cohorts, while they were included only once in the combined cohort using the first date of implantation.

A comparison group for the public hospital implant cohort was composed of women who underwent breast reduction surgery at public hospitals. The identification of this cohort, consisting of 7071 women, is described in detail elsewhere.

Table 1. Characteristics of the Study Cohorts

<table>
<thead>
<tr>
<th></th>
<th>No. of Patients</th>
<th>Age at Entry, Median (Range), y*</th>
<th>Person-Years at Risk*</th>
<th>Length of Follow-up, Mean, y*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Breast Implant Cohorts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private clinic</td>
<td>1653</td>
<td>31 (16-54)</td>
<td>11215</td>
<td>6.8</td>
</tr>
<tr>
<td>Public hospital</td>
<td>1135</td>
<td>31 (13-64)</td>
<td>12810</td>
<td>11.5</td>
</tr>
<tr>
<td>Combined implant cohort</td>
<td>2761†</td>
<td>31 (13-64)</td>
<td>23844†</td>
<td>8.7</td>
</tr>
<tr>
<td><strong>Comparison Cohorts</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Private clinic</td>
<td>1736</td>
<td>33 (13-54)</td>
<td>12051</td>
<td>6.9</td>
</tr>
<tr>
<td>Public hospital breast reduction</td>
<td>7071</td>
<td>31 (11-79)</td>
<td>74401</td>
<td>10.5</td>
</tr>
<tr>
<td>Combined control cohort</td>
<td>8807</td>
<td>31 (11-79)</td>
<td>86452</td>
<td>9.8</td>
</tr>
</tbody>
</table>

*All calculations were based on hospitalizations only.†Duplicate registrations were entered into both cohorts for 27 patients.

between silicone breast implants and CTD have been published.22-46 All112-33,35-40 but one36 have failed to demonstrate an increased risk of systemic sclerosis or any other CTDs. The one study35 that found a small, but significant, excess of CTD was based on self-reporting of diseases, the subsequent validation of reported CTDs found evidence for overreporting, as only 22.7% of the self-reported cases could be confirmed.41 Three independent scientific review bodies have recently evaluated the available data on silicone breast implants42-45; all concluded that an association between silicone breast implants and CTDs has not been demonstrated and is unlikely to exist.

Some investigators46-51 have suggested an association between silicone breast implants and a new atypical rheumatic condition or atypical CTD that does not fulfill established criteria for any known CTD. To date no consensus has been reached as to the diagnostic cri-
All members of the 4 study cohorts were linked to the NRP for data on the occurrence of CTD and other rheumatic conditions. The NRP contains information for virtually every nonpsychiatric hospital admission in Denmark since 1977. Each record includes the PNR, dates of admission and discharge, codes for surgical procedures performed during the admission, and up to 20 discharge diagnoses. Starting in 1995, the NRP also recorded information on outpatient contacts, which includes ambulatory and emergency department visits. Discharge diagnoses were coded according to the Danish modified version of the International Classification of Diseases, Eighth Revision (ICD-8) from 1977 through 1993, and according to a Danish modified version of the International Classification of Diseases, Tenth Revision (ICD-10) of the years that followed.

Women in each cohort were followed up for the occurrence of CTDs and ill-defined and other rheumatic conditions, from the date of the first hospital discharge or outpatient visit for breast implantation, reduction, or other treatments or from January 1, 1977, until the date of death, emigration, or December 31, 1996, whichever came first. Follow-up included ambulatory or emergency department visits from January 1, 1995, through December 31, 1996.

Definite CTD was defined as rheumatoid arthritis (ICD-8: 712.09-39, 712.59; ICD-10: M05, M08.0, M08.2-08.9), dermatomyositis (ICD-8: 716.09, 716.19; ICD-10: M33), systemic sclerosis (ICD-8: 734.00-09; ICD-10: M34), systemic lupus erythematosus (ICD-8: 734.19; ICD-10: M32), or Sjogren syndrome (ICD-8: 734.90; ICD-10: M33.0). 3-5 Ill-defined and other rheumatic conditions included the following: polyarteritis nodosa (ICD-8: 446.09; ICD-10: M30.0), Wegener granulomatosis (ICD-8: 446.29; ICD-10: M31.3), temporal arteritis and polymyalgia rheumatica (ICD-8: 446.30-446.39; ICD-10: M31.5, M31.6, M33.3), psoriatic arthritis (ICD-8: 696.09; ICD-10: L40.5, M07.0-07.3), ankylosing spondylitis (ICD-8: 712.49; ICD-10: M45.9, M08.1), arthritis not further specified (ICD-8: 713.99; ICD-10: M13.0, M13.1, M13.8, M13.9), unspecified rheumatism (including fibromyalgia and myalgia) (ICD-8: 717.90, 717.99, 718.99; ICD-10: M25.5, M25.6, M25.8, M25.9, M62.6, M62.8, M62.9, M79.0, M79.1, M79.8, M79.9), localized scleroderma (ICD-8: 701.01-701.09; ICD-10: L94.0-L94.3), localized (discoid) lupus erythematosus (ICD-8: 695.49; ICD-10: L93.0-L93.2), and/or CTD not further specified (ICD-8: 734.91, 734.99; ICD-10: M31.1, M31.2, M31.4-M31.9, M79.3). Other conditions considered included sarcoidosis (ICD-8: 135.99; ICD-10: D86), Hashimoto thyroiditis (ICD-8: 245.03; ICD-10: E06.3), and amyloidosis (ICD-8: 276.00-276.09; ICD-10: E85).

National hospital discharge rates, including separate rates for ambulatory and emergency department visits, were calculated for definite CTDs as well as ill-defined and other rheumatic conditions by dividing the number of women discharged with these conditions (for first known discharge of the specific diseases) by the mean female population for each 5-year age group and calendar period. The expected numbers of CTDs and ill-defined and other rheumatic conditions were calculated by multiplying the number of person-years of follow-up in the 4 cohorts (Table 1) by the sex-specific national hospital discharge rates for these conditions, for each 5-year age group and calendar period of observation. The ratio of observed to expected cases (O/E ratio) of CTDs and ill-defined and other rheumatic conditions and 95% confidence intervals (95% CIs) were calculated assuming a Poisson distribution for the observed number of diseases or conditions. A direct comparison between the combined implant and the combined control cohorts was also performed whereby the ratio of the O/E ratios from the 2 cohorts, as well as 95% CIs were calculated.

Results for the outcomes under study were similar for both private and public implant cohorts (Table 2) and for both control cohorts; consequently, the implant cohorts were combined as were the control cohorts for analyses (Table 3).

In the combined breast implant cohort, we observed 10 cases of definite CTDs compared with 8.8 expected (O/E ratio = 1.1; 95% CI = 0.5-2.1) (Table 3). Of the 10 observed cases, 8 were rheumatoid arthritis (O/E ratio = 1.4; 95% CI = 0.6-2.7) and 2 were systemic sclerosis (O/E ratio = 3.8; 95% CI = 0.5-13.8). No cases of dermatomyositis, systemic lupus erythematosus, or Sjogren syndrome were observed in the combined implant cohort, with 0.2, 1.4, and 0.9 cases expected, respectively. Ill-defined and other rheumatic conditions had O/E ratios not significantly different from unity, with the exception of unspecified rheumatism (including fibromyalgia and myalgia) (O/E ratio = 1.9; 95% CI = 1.5-2.3) (Table 3). In total (all definite CTDs and ill-defined and other rheumatic conditions), we observed 102 cases in

RESULTS

The age distribution at the time of surgery was similar for the 2 implant cohorts and the reduction cohort, with a median age at first recorded procedure of 31 years, whereas the private comparison cohort tended to be slightly older, with a median age of 33 years at the time of treatment or consultation (Table 1). On average women in the public hospital implant cohort received their implants earlier in the study period than women in the private clinic implant cohort and, thus, the mean follow-up of the hospital implant cohort (mean follow-up, 11.5 years; range, 0-19 years) was longer than that of the private clinic implant cohort (mean follow-up, 6.8 years; range, 0-19 years).

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the combined implant cohort compared with 59.6 expected (O/E ratio = 1.7; 95% CI = 1.4-2.1); excluding cases of unspecified rheumatism brings the observed number of cases to 17 compared with 14.9 expected (O/E ratio = 1.1; 95% CI = 0.7-1.8). Forty-five (44%) of the 102 cases of all rheumatic conditions were identified through outpatient contacts only (definite CTDs, 4 [40%] of 10 cases; unspecified rheumatism, 39 [46%] of 85 cases; and both cases of psoriatic arthritis and CTD not further specified).

In the combined comparison cohort we observed 42 cases of definite CTDs compared with 35.9 expected (O/E ratio = 1.2; 95% CI = 0.8-1.6) (Table 3). In particular there were 26 cases of rheumatoid arthritis (O/E ratio = 1.0; 95% CI = 0.7-1.5), 1 case of dermatomyositis (O/E ratio = 1.1; 95% CI = 0.0-6.3), 2 cases of systemic sclerosis (O/E ratio = 1.1; 95% CI = 0.1-4.0), 7 cases of systemic lupus erythematosus (O/E ratio = 1.6; 95% CI = 0.6-3.2), and 6 cases of Sjögren syndrome (O/E ratio = 1.8; 95% CI = 0.7-1.6) (Table 3). Ill-defined and other rheumatic conditions had moderately elevated O/E ratios for all conditions with at least 1 observed case, although the only condition that reached statistical significance was unspecified rheumatism, for which 238 cases were observed compared with 152 expected (O/E ratio = 1.6; 95% CI = 1.4-1.8) (Table 3). Among private clinic controls a similar excess of unspecified rheumatism was observed in the subgroup who underwent cosmetic surgery other than breast reduction (O/E ratio = 1.4; 95% CI = 0.9-1.9).

In total, we observed 322 cases of definite CTDs and ill-defined and other rheumatic conditions in the combined comparison cohort compared with 217 expected (O/E ratio = 1.5; 1.3-1.7). Excluding cases of unspecified rheumatism brings the observed number of cases to 84 compared with 65 expected (O/E ratio = 1.3; 95% CI = 1.0-1.6). Eighty-six (26.7%) of the 322 cases of all rheumatic conditions were identified through outpatient contacts only (definite CTDs, 9 [21.4%] of 42 cases; unspecified rheumatism, 71 [29.8%] of 238 cases; polyarthritis nodosa, 1 [8.3%] of 12 cases; psoriatic arthritis, 2 [50.0%] of 4 cases; arthritis not further specified, 1 [10.0%] of 10 cases; discoid lupus, 1 [50.0%] of 2 cases; and CTD not further specified, 1 [11.1%] of 9 cases).

Among the other conditions there were no observed cases of polyarthritis nodosa, Wegener granulomatosis, localized scleroderma, localized (discoid) lupus, sarcoidosis, Hashimoto thyroiditis, or amyloidosis in the combined implant cohort. In the combined comparison cohort there were 13 cases of sarcoidosis (O/E ratio = 2.1; 95% CI = 1.1-3.5) and 1 case of Hashimoto thyroiditis (O/E ratio = 0.5; 95% CI = 0.0-2.8) (data not shown), and no cases of localized (discoid) lupus, sarcoidosis, Wegener granulomatosis, localized scleroderma, or amyloidosis. In the direct comparison between the implant and control

*Values indicate the O/E ratio numbers of CTDs and other rheumatic conditions. Obs indicates the number of observations; Exp, the number of observations expected; and 95% CI, 95% confidence interval.

†All values expressed as totals.
cohorts no differences were observed for definite CTDs (odds ratio = 1.0; 95% CI = 0.4-1.7), or for ill-defined and other rheumatic conditions (Table 3).

To assess whether media coverage affected diagnoses, we examined discharge rates for the outcomes under study for the periods January 1977 through December 1991 and January 1992 through December 1996, and found no pattern to suggest an increase in hospitalization for CTD or ill-defined and other rheumatic conditions in the latter period (data not shown).

**COMMENT**

Overall, we found no excess of definite CTDs among 2761 women with breast implants, which is consistent with our previous results, and with those of other epidemiological studies. The total observed number of definite CTDs was close to expectation, as were those for the specific CTDs with the exception of systemic sclerosis, for which the O/E ratio was not significantly elevated. A similar pattern was observed in the combined control cohort, with observed cases of all definite CTDs close to expectation; however, not significantly elevated O/E ratios were observed for systemic lupus erythematosus and Sjogren syndrome, although based on small numbers. Previous epidemiological studies of women with cosmetic breast implants reported risk ratios for definite CTDs combined between 0.44 and 1.24. For individual definite CTDs, in particular systemic sclerosis, previous studies have reported relative risks between 0 and 1.84. Our finding of a not significantly elevated

### Table 3. Observed-Expected (O/E) Ratios for Definite Connective Tissue Diseases (CTDs) and Other and Ill-Defined Rheumatic Conditions Among Women in the Study Cohorts

<table>
<thead>
<tr>
<th>Conditions Among Women in the Study Cohorts*</th>
<th>Combined Implant Cohort†</th>
<th>Combined Control Cohort</th>
<th>Direct Comparison</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>(n = 2740)</td>
<td>(n = 8807)</td>
<td>Implant/Control</td>
</tr>
<tr>
<td><strong>Obs</strong></td>
<td><strong>Exp</strong></td>
<td><strong>O/E Ratio</strong></td>
<td><strong>95% CI</strong></td>
</tr>
<tr>
<td>All definite CTDs</td>
<td>10</td>
<td>8.8</td>
<td>1.1</td>
</tr>
<tr>
<td>Rheumatoid arthritis</td>
<td>8</td>
<td>5.8</td>
<td>1.4</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>0</td>
<td>0.2</td>
<td>0.0</td>
</tr>
<tr>
<td>Systemic sclerosis</td>
<td>2</td>
<td>0.5</td>
<td>3.8</td>
</tr>
<tr>
<td>Systemic lupus erythematosus</td>
<td>0</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Sjogren syndrome</td>
<td>0</td>
<td>0.9</td>
<td>0.0</td>
</tr>
<tr>
<td>Other and Ill-Defined Rheumatic Conditions</td>
<td>102</td>
<td>59.6</td>
<td>1.7</td>
</tr>
<tr>
<td>Polyarteritis nodosa</td>
<td>0</td>
<td>0.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Polymyalgia rheumatica and temporal arthritis</td>
<td>1</td>
<td>0.7</td>
<td>1.5</td>
</tr>
<tr>
<td>Psoriatic arthritis</td>
<td>1</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>Arthritis not further specified</td>
<td>3</td>
<td>2.1</td>
<td>1.5</td>
</tr>
<tr>
<td>Ankylosing spondylitis</td>
<td>1</td>
<td>0.5</td>
<td>1.9</td>
</tr>
<tr>
<td>Discoid lupus</td>
<td>0</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>CTD not further specified</td>
<td>10</td>
<td>8.8</td>
<td>1.0</td>
</tr>
<tr>
<td>All Rheumatic Conditions</td>
<td>238</td>
<td>152.0</td>
<td>1.6</td>
</tr>
<tr>
<td>All rheumatic conditions excluding unspecified rheumatism</td>
<td>84</td>
<td>65</td>
<td>1.3</td>
</tr>
</tbody>
</table>

*Values indicate the O/E ratio numbers of CTDs and other rheumatic conditions. Obs indicates the number of observations; Exp, the number of observations expected; 95% CI, 95% confidence interval; and RR, relative risk.

†All values expressed as totals.
O/E ratio of 3.8 is not in accord with previous studies, but the finding is based on only 2 cases and likely reflects chance.

Considering all rheumatic conditions (definite CTDs and other rheumatic conditions) a significant excess was observed in both the implant and control cohorts, mainly owing to the excess of unspecified rheumatism in both cohorts. Subtracting cases of unspecified rheumatism yielded an O/E ratio of 1.4 in the combined breast implant cohort, and an O/E ratio of 1.3, of borderline significance in the combined control cohort. Among ill-defined and other rheumatic conditions, we previously reported among women with implants an excess of muscular rheumatism, which in the present study is classified as unspecified rheumatism. The present study also found an elevated O/E ratio for unspecified rheumatism among women with breast implants as well as among women in the control cohort. We previously concluded that the excess of muscular rheumatism was related to breast surgery per se, rather than to any systemic effect of silicone breast implants, owing to the fact that similar excesses were observed among women with breast implants and breast reduction. In the expanded study reported herein, an excess was also observed in the private clinic control group, which included women who underwent breast reduction as well as women with other types of cosmetic surgery and women who sought only a consultation. The direct comparison revealed no material difference in hospitalization for unspecified rheumatism between the combined implant and combined control cohorts.

Although outpatient data were available only for the last 2 years of follow-up, these records contributed significantly to the number of observed cases of definite CTDs as well as to cases of ill-defined and other rheumatic conditions, including unspecified rheumatism. Thus outpatient data seem to add considerably to the sensitivity of data from the NRP, and may reduce bias from underreporting of less severe conditions of definite CTD, as well as ill-defined and other rheumatic conditions.

Our study population was well defined and the follow-up virtually complete owing to the use of nationwide hospital and population registers. Information on exposure in the public hospital cohorts had been validated earlier and found to be accurate, and for the private clinic cohorts, exposure was established for all patients through medical record abstraction by 2 of us (K.K. and S.F.). Outcome data for specific CTDs in the original public hospital cohort were validated previously and found to be valid. The systematic national approach with use of register data ensures that disease ascertainment was unbiased. Based on our 95% CIs, we can exclude relative risks for definite CTDs of about 2-fold or higher. However, with the exception of rheumatoid arthritis, we had only limited power to detect an increased risk of any individual CTD. The outpatient data in the NRP from 1995 on enhances the potential to detect milder and/or localized diseases. Although these data were only available for a limited part of the study period, there was no indication of higher risks for women in the implant than control cohorts. No changes in hospitalization pattern after 1992 were observed, indicating that the publicity concerning a potential link between silicone breast implants and CTD beginning in 1992 had little, if any, influence on hospitalization for rheumatic conditions among Danish women with silicone breast implants.

CONCLUSIONS

This study lends further support to the conclusions of earlier investigations and of independent review panels that an association between silicone breast implants and definite CTD has not been demonstrated. The observation of an excess of unspecified rheumatism among women with implants and among control women indicates that women undergoing or seeking cosmetic plastic surgery have rates of unspecified rheumatism in excess of those of the general population. Future studies of atypical CTD among women with breast implants should consider this finding when identifying appropriate control groups.

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