Scientific Committee on Emerging and Newly Identified Health Risks

SCENIHR

The Safety of PIP Silicone Breast Implants

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SCENIHR

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http://ec.europa.eu/health/scientific_committees/emerging/members_committee/index_en.htm

ABSTRACT

Breast implants can fail, regardless of manufacturer, and the probability of failure increases with time since implantation. This phenomenon is true for all types of implants used in humans. In most cases, breast implant failure appears to be without identifiable health consequences for the patient with the exception of possible local complications.

The question asked of the SCENIHR is: Are the breast implants manufactured by PIP more prone to failure than those of other manufacturers, and what are the consequences to health, if any, from PIP implant failures?

In view of the nature and reliability of the available data on breast implants overall and the urgency of an Opinion from the SCENIHR on PIP silicone breast implants in particular, the focus of attention in this initial response is on the following aspects:

- Physical and chemical properties of the PIP silicone breast implants, where accessible
- Findings of the effects of PIP implant contents in the required safety tests, where available
- Reports of incidents of PIP implant failures, where available

It should be noted that PIP silicone breast implants have been found to vary considerably in composition and, as a result they are likely to vary substantially in performance characteristics. No clear temporal trend of implant problems has been identified for PIP silicone breast implants. Consequently it is very difficult to identify a truly representative PIP implant for testing purposes.

i) Physical and chemical properties

The available evidence indicates that many PIP silicone breast implants were manufactured from industrial grade silicone of lower quality than medical grade silicone. This appears to be associated with a higher content of low molecular weight components. As a consequence of the migration of these components it is reasonable to conclude that the shell might be weakened and that components could leak into the surrounding tissue. Tests conducted by the French Authorities on the physical integrity of a sample of PIP silicone breast implants indicated weaknesses in PIP shells not found in other commercially available implants.

ii) Toxicity tests findings

To date, few studies aimed at evaluating the toxicity of the contents of PIP silicone breast implants have been conducted using the tests specified for assessing the safety of grade III medical devices (which includes breast implants). The tests that were performed are designed to assess cytotoxicity, irritancy and genotoxicity. Medical grade silicone gels used in other breast implants gave negative results in these tests.

In the case of the contents of the PIP silicone breast implants, tests for cytotoxicity and genotoxicity were negative. However, an *in vivo* test for irritancy was positive. This indicates the potential for inducing local irritancy (which may manifest as sore and/or enlarged local lymph nodes or sensation in the breast) when the silicone gel is released from the implant. The form that local irritancy might take will depend on the amount released, the duration of exposure and other local conditions. The implications of this positive result in an irritancy test, for women with PIP silicone breast implants are currently uncertain and further investigation is required.

iii) Incident reports

It is important to note that clinical breast examinations alone have little sensitivity for detecting implant rupture. If there are clinical signs of adverse effects, then a diagnostic work-up is mandatory.

There are cases reported suggesting that PIP silicone breast implants may have a higher failure rate in the first few years after implantation compared with those from other breast implant manufacturers. There are also a few case reports that ruptured PIP silicone breast implants may be associated with a higher incidence of swollen and painful lymph nodes in the axilla, the groin, the neck and the mediastinum.

The limited clinical data, along with the absence of epidemiologic data on PIP silicone breast implants provide insufficient evidence to warrant a conclusion that women with PIP silicone breast implants have a greater risk to their health than women with breast implants from other manufacturers. In regard to breast implants in general there is, , a reasonable number of large, good-quality studies showing no increase in any cancer type or connective tissue disease among women with standard silicone breast implants (including women with ruptured implants). However, in the case of PIP implants, when the limited available clinical information is taken together with the findings from tests of the physical and chemical properties of the shell and silicone, and of the *in vivo* irritancy test, some concerns are raised about the safety of PIP silicone such breast implants as the possibility for health effects cannot be ruled out.

Further work is proposed to establish with greater certainty the health risks, if any, that may be associated with PIP silicone breast implants.

Keywords: PIP breast implants, implant failure, safety evaluation, toxicity, silicone

Opinion to be cited as:

SCENIHR (Scientific Committee on Emerging and Newly Identified Health Risks), Breast implant failure, 1st February 2012

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EXECUTIVE SUMMARY

1) The SCENIHR has been asked to address the potential risks from PIP breast implants because, according to the findings of the French Health Authorities, the French manufacturer (Poly Implant Prothèse; abbreviated as "PIP") made use of low-quality material (industrial silicone). In such an assessment, it is important to compare the available information with findings for breast implants from other manufacturers.

2) Important difficulties in making such an assessment are:

   a) The number of patients in the individual member states is unknown due to patient tourism and poor record keeping by the manufacturers of PIP silicone breast implants;

   b) Reporting of breast implant failure and of related adverse effects on health is not obligatory. Consequently, reported incident rates are unreliable. However, even for silicone implants of standard quality, reoperations are needed eventually for a high number of patients.

3) There is no indication from the available data that the group of women who have had PIP silicone breast implants differ significantly from the group having implants from other manufacturers. Overall around 80% of all breast implantations are performed for cosmetic reasons and about 20% for reconstructive purposes. A minor fraction of implantations involve women with congenital malformations.

4) There are various methods to identify implant failure. It is important to note that clinical breast examinations alone have little sensitivity for detecting implant rupture. If there are clinical signs of adverse effects, then a diagnostic work-up is mandatory. A clinical examination is therefore likely to miss implant rupture in the absence of positive signs. There is international agreement among professional radiologists and reconstructive and aesthetic surgeons that Magnetic Resonance Imaging (MRI) is the most accurate modality to detect ruptures. A meta-analysis has estimated the overall sensitivity to 78% (95% CI, 71%-83%) and the overall specificity was 91% (95% CI, 86%-94%). Ultrasonography is the second best imaging modality for detecting ruptures. However, ultrasonography is less precise and more dependent on the human operator than MRI. Mammography is even less useful.

5) Silicone breast implants can fail, regardless of manufacturer, and the probability of failure increases with time since implantation. This phenomenon is true for all the types of implants used in the human body. Most breast implants seem to be rather durable for the first 6-8 years, whereafter the risk of rupture increases. For third generation implants a general rupture risk 10%–15% within 10 years of implantation seems to be an appropriate estimate. Implants with more cohesive silicone seem to have lower risk of rupture.

6) The reported frequency of local complications among silicone breast implant recipients generally ranges between 17% and 36%. Additional surgery after primary implantation as a result of these complications has been reported to range from 10 to 30%. Capsular contracture is the most frequent reason for additional surgery in women with breast implants with frequencies ranging from 2% to 23% in recent reports. Other complications include pain, haematoma and infection.

7) Other possible healths effects of silicone breast implants that have been investigated in epidemiological studies include:

   a) Lymphoma: A causal link between breast implants and lymphoma has not been established.

   b) ALCL: A very rare type of lymphoma, the Anaplastic Large Cell Lymphoma (ALCL) has been found in the scar capsular tissue around breast implants in 60 patients globally. According to the US Food and Drug Administration (FDA), there might be a minimally increased risk to develop this tumour for patients with breast implants.

   c) Breast cancer and other cancers: Several high-quality studies have been conducted and they have provided clear evidence against an increased risk of breast cancer or any other type of cancer. An increased risk of lung cancer found in some studies appears to reflect a higher frequency of smoking among women with implants.

   d) Connective Tissue Diseases (CTDs): Although there were initial reports of associations with various forms of connective tissue disease, subsequent, large-scale epidemiologic investigations provided consistent evidence against these claims.

   e) Effects on offspring: There were a few early case reports of children born to or breastfed by women with silicone breast implants who developed swallowing difficulties, irritability, nonspecific skin rashes, fatigue, and other symptoms. However, subsequent epidemiologic studies of these issues found no evidence of an association.

   f) Immunological effects: Occasionally foreign body reactions have been reported in a small number of women with breast implants.

   g) Suicide and psychological issues: It is a consistent observation that the population of women with cosmetic breast implants exhibits a two- to three-fold higher rate of suicide than similar-aged women in the general population.

8) The risk factors for breast implant failure may be identified as:

   a) Physical and chemical features of the implant;

   b) The implantation procedure;

   c) Time since the implantation;

   d) Patient specific factors, *e.g.*, accidents.

9) This Opinion draws on three sources of data, namely,

   a) An extensive search of the published literature;

   b) Information provided by some Member States, in particular France, and other national authorities;

   c) Incident reports collected by the IPRAS (International Confederation for Plastic Reconstructive and Aesthetic Surgery) network.

   Because of the urgency of a Scientific Opinion from the SCENIHR, the Committee could only consider the readily available data. The SCENHIR is aware that PIP silicone breast implants have been found to vary considerably in composition and, as a result, are likely to vary substantially in performance characteristics. No clear temporal trend of implant problems has been identified for PIP silicone breast implants. Consequently, it is very difficult to identify a truly representative PIP implant for risk assessment purposes.

10) The data available on PIP are inevitably limited at this stage. The focus of attention in this initial response is on the following aspects:

   a) Physical and chemical properties of the PIP silicone breast implants, where available;

   b) Findings of the effects of PIP implant contents in some required safety tests, where available;

   c) Reports of incidents of PIP implant failures, where available.

11) Physical and chemical properties: The more recent PIP silicone breast implants in common with those of other manufacturers comprise a single envelope/shell. The implants consist of an outer highly cross linked elastomer shell filled with a gel withmore limited cross linking. In common with those of most other manufacturers, PIP silicone breast implants were manufactured using the polymer polydimethylsiloxane, also known as silicone. The chemical reaction resulting in gel formation must be controlled because it governs the degree of crosslinking. The more variable this reaction is the greater is the variation of the content of volatile and/or low molecular mass components in the implant

(gel and shell). Use of industrial grade silicone, along with a lesser control of the cross linking process, appears to be associated with a higher content of low molecular weight components in PIP silicone breast implants. As a consequence of the migration of these components, it is reasonable to conclude that the shell might be weakened and that components could leak into the surrounding tissue. Tests conducted by the French Authorities on the physical integrity of a sample of PIP silicone breast implants indicated weaknesses in PIP shells not found in other commercially available implants.

12) Findings in Toxicity tests: A range of assays are available for toxicity testing. For implant devices with which there will be prolonged contact with the patient the most extensive toxicity testing is needed with end-points including cytotoxicity, sensitization, irritation, acute and subchronic systemic toxicity, genotoxicity, and implantation tests. Additional tests may be indicated by the risk assessment that is performed of a certain medical device/constituent and these may include biodegradation and toxicokinetic studies, chronic toxicity, carcinogenicity, immunotoxicity, neurotoxicity and reproductive/developmental toxicity. To date few studies aimed at evaluating the toxicity of the contents of PIP silicone breast implants have been conducted using tests specified for assessing the safety of grade III medical devices. The tests that have been performed are designed to assess cytotoxicity, irritancy and genotoxicity. Medical grade silicone gels gave negative results in these tests. In the case of the contents of the PIP silicone breast implants, tests for cytotoxicity and genotoxicity were negative. However, an *in vivo* test for irritancy was positive. This indicates the potential for inducing local irritancy when the silicone gel is released from the implant. Any effects will depend on the amount released, the duration of exposure and other local conditions. The implications of this positive irritancy test result for women with PIP silicone breast implants are currently uncertain and further investigation is required.

11) Incident reports: There are cases reported suggesting that PIP silicone breast implants may have a higher failure rate in the first few years after implantation compared with those from other breast implant manufacturers. There are also case reports indicating that PIP silicone breast implants may be associated with a higher incidence of swollen and painful lymph nodes not only in the axilla but also in the neck, the groin and the mediastinum, after rupture but sometimes even without rupture.

The limited and selective clinical data along with the absence of epidemiologic data specifically on the PIP silicone breast implants provide insufficient evidence to warrant a conclusion whether these implants pose hazards not identifed among women with implants of standard quality. In particular, the data preclude a conclusion whether women with PIP silicone breast implants have greater risks to their health than women with breast implants from other manufacturers. However, when the limited available information is taken together with the findings from tests of the physical and chemical properties of the shell and silicone, and of the *in vivo* irritancy test, some concerns are raised about the safety of PIP silicone breast implants. The possibility for health effects cannot be ruled out.

12) The SCENIHR is asked to identify the generic risks and benefits of various actions that might be taken to address these concerns. As noted above there are obvious difficulties in providing scientifically based advice because:

a) Regardless of the manufacturer, the failure rate of an implant increases over time;

b) For many women, it is uncertain whether their breast implant is a PIP manufactured implant;

c) Simple clinical examination alone is unlikely to identify those patients with a leaking/ruptured implant.

d) Many PIP silicone breast implants have been inserted by surgeons who are not qualified in plastic surgery. This might be a source of higher failure rates among their patients.

13) It is important to identify, as far as possible, high-risk categories of patients based on the identified risk factors noted above. Key factors including manufacturer, duration of implant in the body of the patient, patient symptoms, and psychological state have been identified. However, these criteria are insufficiently established at present as regards PIP silicone breast implants and a patient-by-patient approach is therefore required. It is important that the potential risks identified in this opinion are considered in the light of the risks involved in prophylactic explantation.

A controlled prophylactic explantation definitely carries less risk than an explantation after rupture or after the onset of symptoms of inflammation and/or lymphadenopathy. Considering the reduced stability of the shell of PIP silicone breast implants, it is possible that the implant will have to be exchanged for most of the women with such implants within the next 10–15 years.

14) The SCENIHR recommends that further work is undertaken as a priority to establish with greater certainty the type and magnitude of health risks, if they exist, associated with PIP silicone breast implants. In particular,

a) A thorough assessment of the chemical composition of a range of PIP silicone breast implants/explants;

b) Further assessment of biological effects of the silicone gel used in PIP silicone breast implants/explants;

c) Further research on PIP explants to identify cause of failure;

d) The development of simple tests that can be used for routine reliable low cost screening to identify ruptures in (PIP) implants;

e) The establishment of a reliable database on Silicone Breast Implant (SBI) and other implant failures and health effects of such failures.

1. BACKGROUND

According to the findings of the French Health Authorities, a French manufacturer (Poly Implant Prothese) fraudulently made use of low-quality material (industrial silicone) different from the one it had declared in the documents submitted for conformity assessment (medical grade silicone).

The company stopped producing breast implants March 2010.

More detailed and regularly updated information can be found on the French authority's websites[1].

The French Health Authorities published recommendations on Friday, 23 December 2011. The French Health Authorities have recommended in particular:

- that any woman implanted with PIP breast implants consult her surgeon;
- the explantation (removal) of the PIP breast implants in case of implant rupture, or suspicion of rupture or oozing.
- that, as a preventive measure, but not as an emergency, the explantation of PIP breast implants is proposed, even in the absence of any clinical sign of implant deterioration.
  For women who refuse explantation, a close medical follow up is recommended;

There is today no common approach in terms of risk management in the different Member States and some Member States have not advised to explant PIP breast implants preventively but to closely monitor women who have received these implants.

It should be noted that during the preparation of this Opinion it became apparent that PIP silicone breast implants were also marketed by another company under the name of M-Implants and Rofil Implant.

2. TERMS OF REFERENCE

In the light of the above considerations and on the basis of the available scientific evidence, the Scientific Committee on Emerging and Newly Identified Health Risks is requested to provide a rapid scientific opinion on 'The safety of PIP breast implants' according to the provisions of Article 2.3 of Decision 721/2008/EC.

In particular, the SCENIHR is asked:

1. To determine whether implanted PIP breast implants could give reasons for concern from the health point of view when compared with state of the art implants, taking into account their structure, composition and detected defects (*e.g.* low quality silicon, single envelop instead of double envelop) and the risk of rupture and oozing they may present;

2. In case reasons for concern related to implanted PIP breast implants are identified, to make a risk/benefit analysis of explantation.

In its assessment the SCENIHR is invited to take into account in particular:

- the global reported incident rate associated with PIP breast implants;
- the comparison of this global reported incident rate compared with other breast implants;

[1] http://www.afssaps.fr/ and http://www.sante.gouv.fr

- the percentage of this global reported incident rate associated with rupture of PIP breast implants;
- the percentage of this global reported incident rate associated with other type of problems (*e.g.*, inflammatory reactions);
- any evidence suggesting that PIP breast implants are more difficult to explant, before or after rupture, in comparison with other breast implants;
- any increased report of lymph node complications associated with the PIP breast implants.

3. BREAST IMPLANTS GENERAL CONSIDERATIONS

3.1. Introduction and background

Breast implants are considered medical devices and as such are subject to both a preclinical and clinical evaluation before market approval is granted. This section provides an overview on the regulatory framework for medical devices and more specifically for breast implants. In addition the history in the use of breast implants is presented.

3.2 Regulatory framework for medical devices

The EU regulatory framework for medical devices is built on three main Directives:

- Council Directive 90/385/EEC2 on the approximation of laws of the Member States relating to active implantable medical devices (hereafter AIMDD),
- Council Directive 93/42/EEC3 concerning medical devices (hereafter MDD), and
- Directive 98/79/EC4 of the European Parliament and of the Council on in vitro diagnostic medical devices (hereafter IVDD).

The key elements of this regulatory framework are detailed below.

Manufacturers shall ensure that the devices they place on the market comply with the legal requirements and do not compromise the health or safety of patients and users.

Before placing them on the market, manufacturers must carry out an assessment of the conformity of their devices. For devices of medium and high risk, the intervention of a third party conformity assessment body, so-called notified body, is compulsory in the conformity assessment before the placing on the market of the device to verify that it fulfils the relevant legal requirements, in particular the applicable essential requirements laid down in the legislation. Breast implants are in the highest risk class (i.e. class III) since 20035 and as such are submitted to the most stringent pre-market review. In particular, the notified body is required to examine either the design dossier regarding the device or a type of a device. Moreover, it must audit the Quality System to ensure that the manufacturer produces devices which conform to the approved design or type. The notified body must periodically carry out appropriate inspections and assessments to make sure that the manufacturer applies the approved quality system. The notified body may pay also unannounced visits to the manufacturer. At the time of a visit, the notified body may, where necessary, carry out or ask for tests in order to check that the quality system is working properly.

Once devices are on the market, manufacturers must notify the relevant national Competent Authority about incidents and shall investigate these incidents and take any corrective action necessary. National competent authorities need to follow specific procedures laid down in the legislation when they consider that an unsafe medical device must be withdrawn from the market ("safeguard clause") or when a CE marking is unjustifiably affixed to a device or missing ("wrongly affixed CE marking").

[2] OJ L 189, 20.7.1990, p. 17
[3] OJ L 169, 12.7.1993, p. 1
[4] OJ L 331, 7.12.1998, p. 1
5 OJ L 28/43, 4.2.2003, p. 43

3.3 Procedure related to CE marking on breast implants

Before affixing the CE marking on a breast implant, the manufacturer must follow a conformity assessment procedure where a notified body intervenes to check the conformity of the product with the applicable essential requirements.

In order to show conformity with the essential requirements a safety evaluation on breast implant materials has to be performed. The safety evaluation should be performed within the context of a risk management process such as described in the international standard EN ISO 14971 for the application of risk management to medical devices (EN ISO 14971: 2009). To minimize the risks involved in the use of the device, all known or foreseeable hazards should be identified, and the risks arising from the identified hazards should be estimated and evaluated. The risks should be controlled by eliminating or reducing them as far as possible, aiming for inherent safety by design. This should be an iterative process incorporating information becoming available from clinical use and post marketing surveillance.

Specific product standards dealing with implants in general and breast implants in particular exist describing specific requirements and testing. General requirements described in EN ISO 14630 (EN ISO 14630:2008 Non active surgical implants – general requirements) include aspects on performance, design, materials, design evaluation, manufacture, sterilization, packaging and information supplied by the manufacturer, Specific requirements for breast impants related to the issues mentioned above are described in EN ISO 14607 (EN ISO 14607; 2007 Non active surgical implants – mammary implants – particular requirements). In this standard the preclinical evaluation of breast implants includes mechanical tests including shell integrity (elongation, tear resistance, strength of joints, seams or seals, and design of shell), valve or injection site competence, filling material (compatibility between filling material and shell, test for silicone gel cohesion), implant resistance (static rupture resistance testing, fatigue resistance testing and impact resistance), volume, dimensions, and surface. In addition, chemical evaluation needs to be done including testing of shell material, silicone elastomer or coated materials, filler materials, and a release test. Furthermore a biological evaluation needs to be performed in accordance with EN ISO 10993-1, and a clinical evaluation in accordance with EN ISO 14155. The biological evaluation is elaborated in section 5.2

3.4 Brief history of breast implants

3.4.1 Implants in general

Silicone breast implants (SBI) were introduced in 1963 in the United States and soon spread to the rest of the western world. For years, the only available types of implants contained silicone membranes and fillings. Later, saline was introduced as a filler, and certain other substances have been tried, but various drawbacks have so far ruled out their widespread use. Breast implants have been modified along the way for improvements on the basis of suggestions by both patients and surgeons (Brody 2009).

There is consensus in the literature to classify implants into generations to indicate certain physical characteristics specific for the types of implants in question. This classification is simplified, but necessary in the scientific literature to compare for instance complications after implant surgery. The most precise grouping into generations would be by characteristics of both the silicone shell/membrane and by the filler silicone (Hölmich *et al.*, 2001). However, since this demands specific information about individual implants, a more practical approach is the categorization according to calendar time. A major confounder is that distributors in different countries have introduced new implant generations at different calendar time. Some manufactures have produced more than

one generation of implants at the same time, and implants can be used for up to 5 years after production (Hölmich *et al.*, 2001).

The initial implants were rather firm both in membrane and gel, the second generation implants were made softer and the membrane less viscous. It became clear that a substantial gel-bleed as well as a high number of ruptures was found in the second generation implants, and modifications were made for improvement, resulting in the subsequent third generation implants. The silicone elastomer was enforced with a barrier layer, which may differ among different products, but the term "low-bleed membrane" or "barrier-coated membrane" is widely used. The gel in third generation implants has again been made somewhat less viscous/ more cohesive. At the same time (about 1989), due to complications with tight scar tissue around implants (capsular contracture), a texturing of the surface was introduced. The third-generation implants, which are still in use, are produced both with a smooth or textured surface (Brody 2009).

High degree of cohesiveness is achieved by increased cross-linking of the polymer silicone gel molecules. This makes the gel firmer, which can be perceived as a disadvantage, however, the implants are more form-stable and anatomical design can be applied, as in the newer, "fourth generation implants". In addition, these implants are considered safer with respect to rupture. The anatomical fourth generation implants were introduced by McGhan in the mid 90's and other companies followed. A "fifth generation" of implants has been introduced with anatomical implants with an even more cohesive gel in the most projecting part of the implant. There is no consensus among manufacturers regarding terminology or classification of cohesiveness, which makes comparisons difficult. Most of the larger companies offer different types of cohesiveness within their repertoire.

For a rupture study, characterisation of implants in a Danish cohort led to the following simplified stratification based on calendar year: First generation implants were used in Denmark in the period 1974–78, second-generation implants in the period 1979–87; and the third-generation barrier-coated, low-bleed implants, which are currently in use, have been available since 1988. The first fourth-generation implants were used in 1994 (Hölmich *et al.*, 2001).

3.4.2 PIP silicone breast implants

The silicone Poly Implant Prosthèses were produced in France since 2001 in its present form. These PIP silicone breast implants have been found to contain an inferior silicone and have not been produced according to the documented procedures provided to obtain CE-mark. They have been available in smooth and textured variants. If classified by calendar time of production and marketing, they would be considered as third generation implants. However, based on reports of a large number of early ruptures, as well as heavy gel bleeds, these implants behave like the older and inferior second generation implants. In addition to the brand name PIP these implants have also been marketed by another company under the name M-implants and Rofil implant.

4 Approach used to develop this opinion

This section describes the various methods used to obtain information on the potential risks associated with the use of silicone breast implants in general and PIP breast implants in particular.

4.1 Search on the published literature on silicone breast implants

The European Commission contracted a search on the published literature on silicone breast implants. The search yielded more than 300 hits.

The aim of this work was to carry out a rapid and comprehensive data examination activity related to the subject of PIP silicone implants from 1998 to present. Virtually all of the extensive published literature on breast implants pertains to silicone gel breast implants in general without reference to manufactuerer. These studies include implants of the earliest generation of implants through to the latest, highly cohesive fourth (fifth?) generation implants. Data specifically addressing safety and health effects of PIP silicone breast implants are extremely limited but will be noted where available.

We have included articles from the peer reviewed scientific literature on:

- Occurrence of various diseases and complications in relation to silicone breast implants in general, including potential links with breast cancer, other cancers, connective tissue diseases, offspring effects and other health effects such as inflammation, irritation and infection.
- Rupture of silicone breast implants in general, including rates/frequency, clinical sequelae as well as complications associated with side effects of both intact and ruptured breast implants.
- Toxicological data on silicone breast implants.
- Information on the toxicity, safety and clinical effects of PIP silicone breast implants.
- Occurrence of health effects of implantation/explantation of silicone breast implants, including medical sequelae, infections and inflammations.
- Information on the composition of silicone breast implants and silicone gels, including additives, stabilizers, impurities and by-products.
- Epidemiological and clinical rupture information on silicone implants destined for the buttocks, testicles, lips.

PubMed was the primary search engine used to find articles from the scientific literature published from 1998 to present. The searches carried out are summarised in the table below.

Search term(s)	**Number of articles**
Silicone breast implants	1,025#
Silicone breast implants (review papers)	130
(Silicone breast implants) AND (breast cancer)	232
(Silicone breast implants) AND (rupture)	148
(Silicone breast implants) AND (intact)	36
(Silicone breast implants) AND (inflammation)	94
(Silicone breast implants) AND (infection)	78
(Silicone breast implants) AND (irritation)	0

(Silicone breast implants) AND (epidemiology)	121
(Silicone breast implants) AND (toxicology)	3
(Silicone breast implants) AND (removal)	110
(PIP implants)	110
(PIP implants) NOT (contraceptives)	37
(Silicone implants) AND (buttocks)	22
(Silicone implants) AND (testicles)	8
(Silicone implants) AND (lips)	17
(Silicone implants) AND (composition)	31
(Silicone implants) AND (impurities)	1
(Silicone implants) AND (additives)	3
(Silicone implants) AND (by-products)	1
(Silicone breast implants) and (stabilizers)	1

Article titles only were checked for the search indicated by hash '#' because of the large number of results obtained. The abstracts of all other articles located were checked and there was found to be considerable overlap between the search results.

Lists of potentially relevant articles have been compiled. The titles and bibliographical data for these articles are given in the tables below. Where available, the research group/expert(s), institute or company details have also been included. Articles which examine the following endpoints/effects have been included in the search results and those which fall into more than one category are indicated by an asterisk '*':

* Review papers on silicone breast implants which have been grouped according to the following categories (where the main topic of the review was clear):
    - Cancer
    - Non-cancer effects
    - Rupture
    - Other;
* Links between silicone breast implants and breast cancer;
* Inflammation and silicone breast implants;
* Infection and silicone breast implants;
* Rupture of silicone breast implants;
* Intact silicone breast implants;
* Composition of silicone implants;
* Toxicological data on silicone breast implants;
* Epidemiological data on silicone breast implants;
* Removal of silicone breast implants;
* PIP implants; and
* Silicone implants in buttocks, testicles and lips.

Where possible, the full papers of the potentially relevant articles have been retrieved. Abstracts only have been provided for articles which fall into one or more of the following categories:

* Those which are Epub ahead of print;
* In languages other than English;
* Unavailable in PDF format for immediate download from the document supplier.

4.2 Information gathering from plastic and aesthetic surgeons' network

The International Confederation for Plastic Reconstructive and Aesthetic Surgery represents almost all Board Certified plastic surgeons in the world (about 40 000) in 102 nations. It has gathered incident reports from Spain, France, UK, Finland, Lebanon, Cech Republic, Italy and Switzerland. From within this network of fully trained plastic surgeons further information regarding PIP and M-implants could be obtained: It is very difficult to identify which patients received PIP silicone breast implants. M-implants continued to be on the market in Eastern Europe *e.g.* Estonia at least until end of October 2011. Patient tourism is very common with patients from Western European nations travel to Eastern Europe and Thailand for surgery at lower expenses, while patients from the Arab world have their surgery in the Western European nations.

4.3 Data provided by member states and other national authorities

The European Commission formally requested submission of relevant data from the Member States and other national authorities. The call was answered without delay by those Member States and other national authorities having data.

5 PHYSICAL, CHEMICAL AND TOXICOLOGICAL PROPERTIES OF BREAST IMPLANT DEVICES

5.1 Physicochemical nature of breast implant devices

5.1.1 The envelope/shell/membrane

Breast implants consist of an outer shell filled with a gel or liquid solution. Most breast implant are manufactured using the polymer polydimethylsiloxane, also known as silicone. Both the shell and the content (filling material) consist of polydimethylsiloxane the level of cross linking between the polymers determining the fluidness/liquidness of the material. The shell consists of a silicone elastomer with a high level of cross linking between the polymers, whereas the filling of the implants consists of silicone gel with a lower level of cross linking (Williams 1996). In addition, fillers may be present notably amorphous silica in the elastomeric shell to increase the tear resistance. It should be noted that besides breast implant a variety of medical devices are manufactured composed of silicone elastomers.

Most implants comprise a single envelope. This envelope may on occasion have small, difficult to detect pinhole defects. Defects such as tiny cracks are sometimes also found where the posterior patch is 'welded' to the remaining implant.

5.1.2 The contents: Chemical composition and physical properties.

Due to its production method all commercial silicone products will contain some low-molecular-weight species as well as the cross linked macromolecules of the polydimethylsiloxane (Williams 1996). These elastomers can have a variety of molecular sizes. In some breast implants water is used as the filling material.

The degree of crosslinking is influenced by the chemistry of the system used, its stoichiometry and last but not least by the mixing and processing conditions (time and temperatures applied). Additionally, the properties of cross-linked silicones are strongly influenced by the amount and surface properties of the nano-silica filler added for sufficient mechanical properties of the silicone rubber.

Dependant on the chemical reaction during gel formation the degree of crosslinking might vary strongly which results in a strong variation of the content of volatile and/or low molecular mass components in the implant (gel and shell). Therefore, one has not only to consider (strong) variation of mechanical properties (viz. modulus, strength and elongation at break) of the shell but also a much faster release of the unreacted silicone components via the shell into the surrounding tissue. However, the amount of such material released depend on the overall concentration of the low molar mass proportion of the components. Therefore, for example a standard medical grade gel (Nusil MED3-6300, Nusil Technology LLC, Carpinteria, CA, USA) is specified with a volatile content of less than 1%.

In addition, the diffusion through the shell is amplified by swelling even for traces of elements, additives, impurities or other components which might be normally trapped in the implant.

This clearly indicates that additives/components beyond those of medical grades might be released from the implant and yield unexpected tissue reactions. For example the

Nusil Med3-6300 is approved with respect to trace elements according the existing guidelines (ASTM E 305).

As the breast implant is subjected to a dynamic load fatigue properties have to be investigated as well. They are known to be decreased by low molar mass media.

Platinum is used as a catalyst in silicone elastomers to start crosslinking. Slightly elevated levels of platinum at the zero oxidation state have been found sometimes for women with implants compared to a control group but no clinical consequences are expected due to the known toxicity of Pt at oxidation state zero (Brook 2006), therefore, leaching of platinum from the breast implant is not an issue. On the other hand potential impurities which cannot be excluded when components are used which do not fulfil medical grade specifications might result in oxidation states of Pt being toxic (Maharaj 2004). Utilizing non medical grade silicone components increase the risk of having traces of heavy metals beyond the Pt *e.g.* tin (Sn), zinc (Zn), chromium (Cr), arsenic (As), lead (Pb), antimony (Sb), nickel (Ni), Copper (Cu). In relation to heavy metals the FDA recommends to analyse these in the "Guidelines for Industry and FDA staff" (FDA 2006).. In the same Guideline extractables and releasable chemicals from the implants are recommended to be analysed. It is evident that the extractables and releasable components as described above are strongly depending on the production process and its controlled reliability with respect to a responsible quality management. For the case under consideration (PIP silicone breast implants) these requirements on the process are not fulfilled.

In general, silicone elastomers and gels need to be carefully investigated before approving them for any utilization, in particular a medical one. For example it is known that poly(dimethylsiloxane) (silicone rubber) has poor mechanical properties in the unfilled state, which are improved by the incorporation of mineral filler (Bokobza 2004). The mineral filler (mostly nano and micro scaled) can be an additional effective source for the above described heavy metals, due to their large specific surface.

5.2 TESTING PROCEDURES ON DEVICES

5.2.1 BIOLOGICAL EVALUATION OF MEDICAL DEVICES

Toxicological hazards associated risk can be identified by determining the biocompatibility of medical devices or their constituents by applying the EN ISO 10993 series dealing with the biological evaluation of medical devices (ISO, Geneva, Switzerland, CEN, Brussels, Belgium). These standards provide an approach to the biological evaluation of medical devices that combines the review and evaluation of existing data from all sources with, when needed, the selection and application of additional tests, thus enabling a full evaluation to be made of the biological responses to each medical device, relevant to its safety in use. A framework is included for the evaluation and safety testing based on the contact (exposure) time during clinical use.

An important first step in the safety assessment process is a proper and detailed characterisation of the material to be tested. Such characterisation should identify constituent chemicals of the device and possible residual process aids or additives used in its manufacture. This information on the chemical composition of a material may permit identification of potential health hazards before toxicity testing has been initiated This is based on previous testing of the same or very similar materials that has been conducted previously, and/or from information that might be available in the scientific literature. Another important component of the safety assessment process, and establishing whether there exist risks to human health, is a detailed consideration of the patterns of exposure that are likely to occur to various components of the device. In addition to this classical safety evaluation for chemical constituents, a safety evaluation

of the final products and/or solid materials relevant to their intended use needs to be performed.

For the identification of any additional testing that may be necessary guidance is provided on the possible assays that may need to be performed for the safety evaluation of a medical device or its constituents. The testing that needs to be considered is based on the use of a medical device (on the surface, as external communicating device, or as implant), the contact site (mucosal surfaces, blood, or tissues), and the contact time (limited (≤24h), prolonged (>24h but ≤30 days), and permanent (>30 days)) (EN ISO 10993-1: 2009, EN ISO 10993-1:2009/Cor 1:2010). It should be realized that depending on the type of medical device and its application, a range of assays can be selected. For implant devices with prolonged contact the most extensive toxicity testing is indicated including cytotoxicity, sensitization, irritation, acute and subchronic systemic toxicity, genotoxicity, and implantation tests. Additional tests may be indicated by the risk assessment that is performed of a certain medical device/constituent such as biodegradation and toxicokinetic studies, chronic toxicity, carcinogenicity, immunotoxicity, neurotoxicity and reproductive/developmental toxicity. A comparison with a well known existing and accepted medical device/material considered to have an acceptable risk may be used in the safety evaluation of a newly developed medical device/material to determine the relative risk. Ultimately,the final risk assessment incorporating all information available including data obtained by testing needs to be taken into consideration to establish both the potential health risks and the likely benefits that will derive from the use of any particular medical device.

5.2.2 Specific test for breast implants

As noted above (see section3.3) the preclinical evaluation of breast implants includes mechanical tests such as shell integrity (elongation, tear resistance, strength of joints, seams or seals, and design of shell), valve or injection site competence, filling material (compatibility between filling material and shell, test for silicone gel cohesion), implant resistance (static rupture resistance testing, fatigue resistance testing and impact resistance), volume, dimensions, and surface. In addition, chemical evaluation needs to be done including testing of shell material, silicone elastomer or coated materials, filler materials, and a release test on leakage.

5.2.3 Toxicology of silicones

The basic material of silicone breast implants, dimethylsiloxane, is widely used in many industries, various consumer products and medical devices. The various applications may have their specific composition of the silicones, *e.g.* oily products used as lubricants containing low molecular weight oils, and solid elastomers used in various products consisting of highly cross linked polymers. For medical devices medical grade silicones are used which contain a reduced content of low molecular weight polymers. So, in general dimethylsiloxane is considered acceptable safe for human use. Already in 1999 the Institute of Medicine (Washington, USA) conducted an extensive evaluation on the safety of silicone breast implants. In general, the committee concluded in 1999 that the review of the toxicology studies of the silicones known to be used in breast implants does not provide a basis for a health concern at expected exposures. Local complications with silicone breast implants were considered the primary safety issue (Bondurant *et al.*, 1999).

5.3 PIP findings

In 2010 several laboratory studies were performed according to the currently applicable ISO/CEN standards, on retrieved PIP silicone breast implants by the French Health Authorities (AFSSAPS). These tests included testing on silicone chemical composition, shell strength and integrity, and a limited toxicological evaluation.

i) PIP findings

PIP silicone breast implants were made with three different types of shells (smooth, textured, and micro textured) and at least three different types of gels (NUSIL, PIP1, and PIP2). PIP1 gel was used before 2008, and PIP2 gel was used after 2008. In addition the barrier layer was removed from the shell in 2007. So there are many types of PIP silicone breast implants that have been marketed.

The silicones used in PIP silicone breast implants were not the CE marketed Nusil (MED3-6300) that was indicated as component in the files on PIP silicone breast implants. The Nusil silicones were substituted by other types of (industrial) silicones. The characterization of the raw materials showed that two kinds of silicone gel were used for the filling of PIP prostheses. These raw materials were different from the Nusil gel that was described in the dossier filed by the company. The PIP silicone gels contained significant levels of silicones with low molecular mass. In addition, thermographic analysis showed that the PIP gels were much less stable than the Nusil gel. Regarding the release of silicones considerable variability was observed reflecting a poor reproducibility of the manufacturing process.

Twelve controls (unimplanted implants or preimplants) were mechanically tested—6 textured and 6 smooth implants. The tests for elongation-at-break showed the textured implants were non-compliant, and the smooth implants were compliant. There is no standard for compliance for force-at-break. However, the average force-at-break for textured implants was lower than the average force-at-break for smooth implants. Smooth and textured implants were fatigued tested using the CE Mark technique, and both types were compliant after 2 million cycles. The results of the tensile test and fatigue resistance test comply with the standards (EN ISO 14607). Mechanical tear elongation tests yielded results incompatible with the standard. No cutting, tearing or cracking was observed in PIP silicone breast implants.

The biocompatibility testing was performed according to the EN ISO 10993 series and yielded the following results.

In vitro cytotoxicity testing revealed that the silicone gels used in the PIP silicone breast implants showed no or negligible minimal (<3%) cytotoxicity.

Overall, the genotoxicity of extracts from the gel within the breast implants was investigated in valid genotoxicity tests for the 3 endpoints of genotoxicity: gene mutations, chromosome aberrations and aneuploidy. Samples of the gel were collected from the interior of the implants, after removal of a small part of the shell/membrane of the implant. Extracts of theses samples were obtained by either extraction with 0.9% NaCl or DMSO. The extracts did not induce an increase in the mutant frequency in a gene mutation test in bacteria. A genotoxicity test with mammalian cells was not performed. Exposure of human lymphocytes to the extracts did not result in an increase in cells with chromosome aberrations. The absence of a clastogenic effect was confirmed both in an *in vivo* Comet assay in female mice and in an *in vivo* micronucleus test. In both tests a biologically relevant increase in DNA damage was not observed.
Consequently, based on the present reports the extracts from the gel of PIP breast implants can be considered to have no genotoxic potential. This also indicates that any putative carcinogenic effect of the extracts is due to a non-genotoxic mechanism.

The results of the intra-dermal irritation tests performed showed an irritant potential of the PIP silicone gel that was not found with the silicone gels from other prostheses, nor on the gel declared in the manufacturer's dossier.

ii) Explants

Apparently, no PIP explants have been tested. PIP explants should be tested using the procedure outlined in section 5.7 recommendation for future work.

iii) Additional considerations on PIP implant/explant testing

Any investigation into the effects of implantation time on the durability of implants should separate the implants according to type, so that explants can be compared with the proper controls. This is necessary because the strength of implants can vary considerably according to the manufacturer, the implant type, and the lot-to-lot variability for the given type. For this reason control implant data should be presented with the explant data wherever possible.

There is a lack of testing and analysis on all types of PIP silicone breast implants. Preimplants should be tested and analyzed using the protocol recommended in this report for explants. Mechanical testing should also include patch strength testing and fatigue testing.

Rigorous cyclic fatigue testing should be conducted on preimplants to provide information on the fatigue characteristics of the implants. Fatigue testing should be conducted on the worst case, final, sterilized implants with the thinnest shells allowed by the design release criteria using flat plates that cyclically compress the implants. The implants should be fatigued tested at varying loads or displacements to generate an applied force versus number of cycles to failure (AF/N) curve for each type of implant tested. A minimum of 3 implants from a typical production run should be tested at a given load or displacement. The endurance load (the load at which implants do not fail under cyclic loading) should be established at a minimum of 6.5 million cycles run out. The fatigue data should then be used to predict the fatigue lifetime of the implants

5.4 Conclusions

With regard to the testing of the physical, mechanical and biological or toxicological aspects of silicone breast implants a series of assays is available that can guarantee that the implants used have an acceptable low risk for consumers. Silicones (dimethylsiloxane) in general and thus also the ones used in silicone breast implants contain a certain fraction of low molecular weight polymers that may leach from the implants. These low molecular weight components induce swelling of the elastomeric shell of the implant resulting in weakening the strength of the shell. In addition such silicones may be released from the implant by sweating or leakage after damage or rupture of the implant. In these circumstances also other contents like residual additives or impurities may be released from the implant.

Overall the toxicology studies of medical grade silicones known to be used in breast implants do not provide a basis for a health concern at expected exposures. Local complications with silicone breast implants can be considered the primary safety issue.

The testing of PIP silicone breast implants performed so far shows that the quality of the materials used is not according to the standards for breast implants regarding the elastomeric shell used and the silicone gel filling. A relatively high content of low molecular weight components was present. For the silicone gel filling the genotoxic tests performed showed negative results and cytotoxicty was negligible. The PIP silicone gel was shown to be an irritant in an invivo irritation assay. Especially the latter finding indicates the potential for inducing local tissue reactions when the silicone gel is released from the implant.

6 DATA ON IMPLANT FAILURE RATES AND CONSEQUENCES

Tradition and presumably national trends exist as to which kind of breast implants to use for which kind of procedures. The use of different types of breast implants in European countries is presumably quite similar, although specific brands probably differ among nations. The preference of anatomical implants for reconstructive purposes seems

similar, evaluated by presentations at international meetings. In Denmark, the overall majority of implant is textured silicone implants. For reconstructive purposes, most surgeons use anatomical implants with a high cohesiveness gel. For cosmetic augmentation, most use round implants, but some also use anatomical implants. In the US most plastic surgeons prefer smooth implants, the anatomical implant has not been approved for general use yet, and saline filler is still used in about half of the implants**.**

Based on figures from the Danish Registry for Plastic Surgery of the Breast (Henriksen *et al.*, 2003) and the American Society of Plastic Surgeons (ASPS) (Brody 2009) about 20% of all breast implantations are performed for reconstructive purposes and 80% for cosmetic purposes. A minor proportion concerns congenital malformations.

6.1 User groups and their characteristics

6.1.1 Cosmetic purposes

Women seeking cosmetic breast implantation are generally healthy, normal weight to slim, having given birth, and are on average 32 years old (range, 15-60 years). More women receiving cosmetic breast implants are smokers compared to the back ground population, although national differences are likely (Kjøller *et al.*, 2003, Fryzek *et al.*, 2000, Henriksen and Olsen 2002).

6.1.2 Reconstruction surgery

Women undergoing breast reconstruction are either former breast cancer patients (in case of secondary reconstruction) or patients undergoing reconstruction at the time of their mastectomy (primary breast reconstruction). This group includes women with invasive breast cancer and women with in situ cancer in addition to women with a familial disposition to breast cancer, who undergo prophylactic mastectomy and reconstruction.

Breast cancer patient are generally fairly healthy patients besides their cancer. Most patients are free of their illness at time of reconstruction, or in case of primary reconstruction the disease is considered local, or perhaps local-regional. Most breast cancer patients receive adjuvant chemotherapy or endocrine therapy and some also radiation therapy. The average age at time of reconstruction in a Danish registry based material, was 50 years, with a range of 21-72 years (Henriksen and Olsen 2002)

In (former) breast cancer patients undergoing reconstruction the soft tissue layer over the implant is much thinner than in augmented women. The tissue is often quite tight , and in case of previous radiation therapy the tissue is always more fibrotic and un-elastic than if radiation therapy was not used.

It is well known that complications after implantations are much higher in the breast reconstruction cohort than among augmented patients (Henriksen *et al.*, 2005, Cunningham and McCue 2009, Spear *et al.*, 2007). This is multi factorial, for instance due to the operation technique, the amount of tissue available, the laxity of the tissue, the concomitant surgical trauma of mastectomy in primary cases, former tissue damage in case of chemotherapy and radiotherapy in secondary cases.

No studies have compared women with breast augmentation with women with reconstructed breasts with regard to vulnerability. Several good explanations for the different profile of complications exist, but some may in fact be due to different vulnerability in general and perhaps also due to tissue specific factors.

No scientific studies are available to indicate if for instance former breast cancer patients would be more likely to get symptoms from a PIP implant rupture than cosmetic breast augmented patients.

6.2 Methods for identifying failure of breast implants

6.2.1 Clinical diagnosis

Clinical breast examinations have little sensitivity for detecting implant rupture; only positive signs provide useful information, but lack of findings does not rule out implant rupture. In order to exclude implant rupture in the absence of positive signs, more sophisticated diagnostic tools such as MRI are needed, in line with the findings of other studies (De Angelis *et al.*, 1994, Middleton 1998, Hölmich *et al.*, 2005).

Positive signs of implant rupture that sometimes can be detected at physical examination are softened breast consistency or palpable nodules or masses adjacent to the implant (Cohen *et al.*, 1997, Hölmich *et al.*, 2005). Enlarged lymph nodes in the nearest axilla does not necessarily correlate to implant rupture, as enlarged nodes can be found in association with intact implants due to short chain silicone gel migration (sweating). However, taking the patients history into account can add valuable information: a sudden swollen lymph node which also may be sore can be the sign of a new rupture (Ahn and Shaw 1994, Brown *et al.*, 1997, Shaaban *et al.*, 2003).

6.2.2 Magnetic resonance imaging

There is international agreement that Magnetic Resonance Imaging (MRI) is by far the most accurate modality for diagnosing breast implant rupture. In scientific validation studies it has been found to detect silicone breast implant rupture with very high accuracy; with an up to 99% positive predictive value as compared with diagnosis at surgery (Hölmich *et al.*, 2005). Implant rupture is characterized by the linguine sign showing that the breast implant contains multiple curvilinear low-signal-intensity lines within the high-signal-intensity silicone gel (Safvi 2000). The lines are usually scattered diffusely and appear as long strands of decreased signal intensity curved on top of each other. In other studies, comparable or a slightly lower accuracy was found (DeAngelis *et al.*, 1994, Everson *et al.*, 1994, Ahn *et al.*, 1994, Berg *et al.*, 1995, Morgan *et al.*, 1996, Quinn *et al.*, 1996, Soo *et al.*, 1997, Middleton, 1998, Ikeda *et al.*, 2000). A meta-analysis estimated the summary sensitivity to 78% (95% CI, 71–83) and the summary specificity was 91% (95% CI, 86–94) (Cher *et al.*, 2001).

Performance of MRI in a screening setting with much lower prevalence of implant rupture than in the above validation studies is bound to be less precise, but this has not been studied in a prospective setting (McCarthy *et al.*, 2008). In general, the higher sensitivity a method is aiming for, the lower becomes the specificity, and false positives as well as false negatives increase in a setting with few ruptures (McCarthy *et al.*, 2008, Song *et al.*, 2011).

6.2.3 Ultrasonography

Ultrasonography is the second best imaging modality for detecting implant rupture, but it is less precise and more operator dependent (Ahn *et al.*, 1994, Gorczyca *et al.*, 1998, Ikeda *et al.*, 2000). But since the price of an ultrasonography is much lower than MRI it is probably used much more often, and has in clinical algorithms been used as first choice examination (Song *et al.*, 2011, Chung *et al.*, 1998).

6.2.4 Conclusions

When using MRI or ultrasonography, the criteria used to diagnose rupture are very important. Consensus exists (based on validation studies) that certain signs are diagnostic (linguine sign, subcapsular lines etc.). In some cases, specific signs may give suspicion of rupture. However, a conclusive diagnosis cannot be made. Therefore most studies classify results as **certain ruptures, possible ruptures and intacts**, and this is also applicable in a clinical setting. Mammography is not useful to evaluate the implant;

structures within the implant cannot be seen. Extracapsular silicone can be seen on a mammogram.

It should be noted that the only country with specific recommendations for diagnosis of implant ruptures is the US: here a baseline MRI is advised 3 years after implantation and then every 2 years.

6.3 Failure of breast implants in women

6.3.1 Terminology

Differences in diagnostic criteria and implant time in situ likely account for the large discrepancies in the reported number of ruptures in different clinical studies. A certain terminological confusion exists in the literature, making direct comparisons of studies difficult. A frank rupture with a visible defect in the silicone membrane is unequivocal; however, smaller defects, known as 'pinhole defects', can be missed unless the implant is examined carefully. Gel-bleed or gel-sweat is the diffusion of short-chain silicone oils over an intact silicone membrane, so that an oily, slippery surface is a normal finding during explantation of intact first- and second-generation implants (Dowden 1993). Third-generation implants have a so-called 'low-bleed membrane', designed to diminish such diffusion. Sticky silicone with thread-like formations on the outside of the membrane can be mistaken for gel-bleed but in fact indicates a rupture, as the long-chain silicone molecules which are responsible for the thread- like formations cannot diffuse through an intact membrane (Peters *et al.*, 1994, Peters *et al.*, 1999, Dowden 1999, Hölmich *et al.*, 2005). Some authors have grouped implants with gel-bleed with ruptured implants, and some have presumably not differentiated between gel-bleed and tiny ruptures (Robinson *et al.*, 1995, Beekman *et al.*, 1997).

Ruptured or failed implants should only include implants with ruptures – not gel-bleed or sweating. Whether a ruptured implants shell has large or small holes can be of academic interest, but is not necessarily clinically relevant, although the amount of free silicone affects the effort required to remove it from the implant pocket.

Ruptures can be **intracapsular**, meaning that the free silicone gel is present outside the implant but kept within the intact fibrous capsule which forms around the implant. Intracapsular rupture can go unrecognized as there may be no accompanying change in the configuration of the breast, no patient complaints, and no physical diagnostic finding. In an **extracapsular rupture**, free silicone is found on the outside of the fibrous capsule, typically adjacent to the capsule as nodules or lumps. Such lumps contain free silicone surrounded by inflammatory cells, especially macrophages. The terms intra- and extracapsular rupture is mainly used in imaging, whereas clinical evaluation can be less clear.

A **silent implant rupture** is a rupture which was not suspected clinically or from the patients symptoms, but discovered at imaging or surgery. Such ruptures are not noticed because the leaking silicone is kept in place by the surrounding fibrous scar membrane (the fibrous capsule), which has adapted its shape from the implant and no visible re-absorption occurs.

The number of ruptured implants in a specific group of women is denoted the proportion of ruptures. The rupture rate is expressed in time and this indicates that observation period is involved; i.e.; number of ruptures per capita per year or number of ruptures per 100.000 women-years etc – comparable to other incidences. In most literature about ruptures, rupture rate is used instead of rupture proportion, and the quantity is expressed as a percentage. This is not correct, but common.

6.3.2 Time to rupture

It is well established that the rupture of breast implants tends to increase with the time since implantation. There is some indication that PIP devices have an increased likelihood to rupture at earlier times than breast implants from some other manufacturers. This observation needs confirmation.

6.3.3 Causes of failure

Breast implants can fail for a variety of reasons including: (1) inadvertent instrument damage during surgery, (2) open capsulotomy, (3) closed capsulotomy, (4) needle biopsy or hematoma aspiration, (5) shell wrinkling, (6) trauma, (7) mammography, (8) implantation surgery, (9) explantation surgery, (10) manufacturing defects, (11) cyclic fatigue, and (12) patch detachment.

Wear patterns that create pinhole defects have been identified around creases and folds, and areas of folded membrane have been shown to be significantly weaker than adjacent unfolded membrane (Brandon *et al.*, 2001, 2006, Richardson *et al.*, 2002).

Implant ruptures can take many forms, from a small pinhole defect to larger tears in the membrane. Defects are sometimes found in an area where the posterior patch is 'welded' to the remaining implant. Old implants can present with an almost disintegrated membrane. In 1988, Van Rappard and co-workers used a simple test to show that the breaking pressure of explants was negatively correlated with time after implantation. They also found that the pressure used for closed capsulotomy tended to exceed the breaking pressure in older implants, sufficient to cause implant rupture (Van Rappard *et al.*, 1988).

Studies on the mechanical properties of implants have shown mixed results, some indicating a decrease in membrane strength with increasing implantation time (Phillips *et al.*, 1996, Greenwald *et al.*, 1996) but with significant variation by brand, type and even within lots (Phillips *et al.*, 1996, Greenwald *et al.*, 1996, Brandon *et al.*, 2001b, Marotta *et al.*, 2002). A consistent finding is swelling of the membrane, due to uptake of silicone oils or serum lipids, which reduces shell strength (Marotta *et al.*, 2002, Adams *et al.*, 1998, Brandon *et al.*, 2003, Birkefield *et al.*, 2004). After a time, equilibrium sets in and no further swelling or decrease in strength is found, at least in Dow Corning implants (Brandon *et al.*, 2003). After the oils have been extracted, however, the original strength of the membrane is more or less regained in comparison with controls from the same lot that have never been implanted, indicating that the membrane is not 'dissolved' by such swelling (Brandon *et al.*, 2002, Lane and Curtis 2005, Taylor *et al.*, 2007). Some authors have other results (Marotta *et al.*, 2002) and, from a clinical point of view, it is difficult to understand why some membranes do not deteriorate over time, while in other cases very fragile, gelatine-like membranes must be picked out piece by piece during explantation. However, this can be explained by considering shell strength characteristics. Breast implants fail due to the mechanisms that generate damage to the shell. Daily activity body motion, such as walking and running, induces forces on implants. These *in vivo* forces are cyclic and repetitive. Over time the cumulative *in vivo* cyclic loading induces damage to the implant which can result in failure. The rate of damage accumulation can be accelerated for implants with thin or structurally weak shells at the time of implantation. Increased shell swelling can also accelerate the rate of damage accumulation that subsequently could result in shell failure.

6.3.4 Silicone implant survival and rupture

6.3.4.1 Implant survival

Attempts have been made to estimate implant survival by pooling data on explantations (Robinson *et al.*, 1995, Beekman *et al.*, 1997, Goldberg *et al.*, 1997, Marotta *et al.*, 1999). As described in detail below, the use of prevalence data to estimate rupture incidence is problematic. It is at best a surrogate for incidence, and selection bias is a significant risk in such studies. On the basis of their 'master failure curve' based on data from 35 studies with more than 8000 explants, Marotta *et al.* (1999) conducted a retrospective failure analysis for explanted silicone gel-filled breast implants (8000 explants from 35 studies) and found a statistically significant correlation between implant duration and elastomer shell failure (25% within 3.9 years and 71.6% at 18.9 years). An update of that analysis (9774 explanted implants from 42 studies) revealed 26% failure at 3.9 years, 47% at 10.3 years, and 69% at 17.8 years (Marotta *et al.*, 2002). These percentages were arrived at by studying only women who elected to undergo explantation. Because women with severe enough complaints to undergo explantation likely have much higher rupture rates than asymptomatic women, the reported rupture prevalence rates overestimate the rupture prevalence for all women with implants, as asymptomatic women are usually not part of the studies. Marotta *et al.* found a general reduction in tensile strength, tear strength and elongation of explanted silicone elastomer shells and concluded that their explant rupture data are representative of the implant aging properties and rupture characteristics of the general population of silicone gel-filled breast implants that remain implanted. The fact that prevalence of rupture increases over time is not surprising since prevalence is a cumulative measure at a given moment in time. This, however, does not mean that the *probability* of rupture during a specified time period (incidence) increases with increasing implant age, a conclusion that cannot be drawn from the highly selected cross-sectional data analyzed by Marotta *et al.* (2002). This study has also been criticised for biased reporting of the literature(Young *et al.*, 1998, Cook *et al.*, 1999,2002).

Goodman *et al.* reported a meta-analysis of data on explants but used a stricter method, including only the results of five explantation studies (Goodman *et al.*, 1998). Separate Kaplan-Meier survival curves were presented for each study, some of which were within range of that shown in Figure 2 (see below). The study was criticised for not including information about implant generation, as there are large differences in design and durability (Peters *et al.*, 1999). Peters, in a response to this study, showed the survival curves for second-generation implants at his centre; clear differences were seen by manufacturer, Surgitek implants being significantly less durable than Heyer-Schulte and Dow Corning implants, in line with findings in the Danish prevalence study (Peters *et al.*, 1999, Hölmich *et al.*, 2001).

6.3.4.2 Implant rupture

Estimates of breast implant rupture prevalence range widely, in part because the methods of estimating rupture prevalence rates differ among studies (Bondurant *et al.*, 1999; Brown *et al.*, 2000; Handel *et al.*, 2006; Heden *et al.*, 2006a, 2006b; Marotta *et al.*, 1999, 2002; Robinson *et al.*, 1995; Slavin and Goldwyn, 1995). Determination of the frequency of gel migration outside the fibrous capsule is more difficult than ascertainment of rupture prevalence, unless there is implant retrieval (which is usually done in symptomatic women) and examination of explant and tissue.

An MRI study of almost 300 women (533 cosmetic breast implants) randomly picked from a larger study base underwent MRI in 1999, with a median implantation time of 12 years at MRI (Hölmich *et al.*, 2001). This study established the baseline prevalence of implant rupture among a random sample of women with silicone breast implants. A large number of implants were found to be ruptured (26% of implants, and found in 36% of

women. An additional 6% of implants were given the diagnosis of possible rupture). Of the ruptures, 31 (22%) were extracapsular, affecting 23 women (8%) in the study group. Extracapsular rupture was significantly associated with a prior closed capsulotomy. Rupture prevalence was correlated with implant generation, time in situ and also brand (Dow Corning, McGhan, Eurosilicone, Surgitek, and about 100 unknown implants were examined).

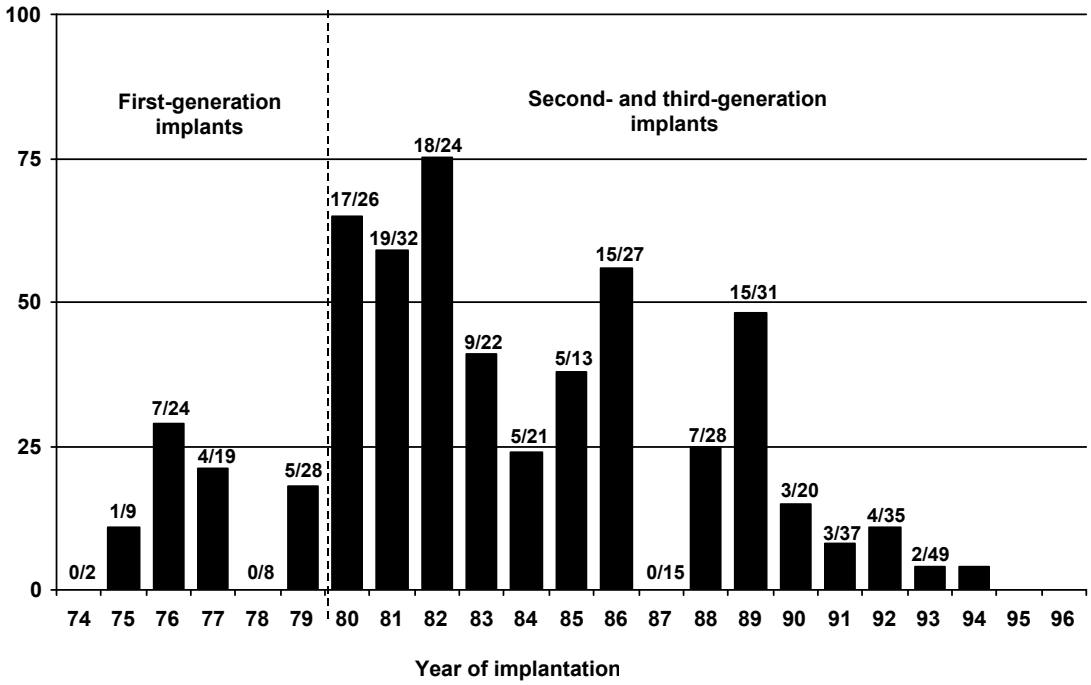

Figure 1: The proportion of ruptured implants at the baseline MRI examination by year of implantation. Figures on top of bars indicate that for instance 18 of 24 implants examined from that particular year were ruptured at MRI (Hölmich *et al.*, 2001).

In a US FDA-funded study published shortly before the Danish prevalence study, Brown *et al.* also examined the prevalence of rupture diagnosed by MRI among a selected group of 344 women with silicone breast implants from two plastic surgery clinics (Brown *et al.*, 2000). The authors found that 69% of the women had a definitely ruptured implant, compared to the Danish 36%. The median implant age at rupture was estimated to be 10.8 years. Extracapsular migration of gel was seen in 85 (12.4%) breasts in 73 (21.2%) of the women. This discrepancy between these and the Danish results is probably due to differences in the types of implants examined: Brown *et al.* examined mostly second-generation implants and a much higher proportion of Surgitek implants (70% vs. 15% in the Danish study). The latter were found to have the highest prevalence of rupture of all the brands studied (Brown *et al.*, 2000).

Handel *et al.* (2006) conducted a study of 1529 consecutive women who received 3494 implants (1137 saline-filled, 778 double lumen, 1537 silicone gel- filled, 38 other) for augmentation, reconstruction or revision at a clinical practice between 1979 and 2004. Rupture diagnosis was based on clinical confirmation at the time of explantation and not on the basis of mammography, ultrasound or MRI findings. After a mean follow-up of 37.4 months (range, 0-23.3 years), silicone implant ruptures occurred in 14 of 1,123 smooth implants, six of 618 textured implants, and eight of 568 polyurethane foam-covered implants, yielding crude prevalence rates of 1.2%, 1.0% and 1.4%, respectively.

MRI rupture screening of 144 Swedish women with 286 fourth generation cohesive silicone breast implants yielded a rupture prevalence of 0.3-1.0% at an average of 6 years post-implantation (Heden *et al.*, 2006a). In a recent multi-center European study, MRI examination of rupture in women with 199 third generation silicone gel-filled breast implants with a median implantation time of almost 11 years revealed a rupture prevalence rate of 8% (Heden *et al.*, 2006b).

It is difficult to compare the results of cross-sectional rupture prevalence studies, for several reasons. Studies often include women with different generations of implants (often not the third or fourth generation single-lumen silicone gel-filled implants currently in use), saline and silicone implants, and implants made by different manufacturers. Studies of rupture prevalence are also likely biased in favor of higher rupture prevalence, since many publications present rupture data for implants that had already been explanted because rupture was suspected. Moreover, studies present data on women with different follow-up periods, and determination of rupture has been based on different detection methods (*e.g.*, explantation, ultrasound, mammography, MRI, clinical survey results in patient cohorts), all with varying sensitivity and specificity. As a result, findings cannot be generalized to the universe of all women with breast implants.

Implant age has been commonly noted in the literature as a determinant of rupture, with risk of implant rupture increasing with implant age (De Camara *et al.*, 1993; Feng and Amini, 1999; Holmich *et al.*, 2003; Rohrich *et al.*, 1998). Holmich *et al.* (2001) found that age of implant was significantly associated with rupture prevalence among second and third generation implants. However, despite the small number of first generation implants, the prevalence of rupture among first-generation implants, which had thick shells and highly viscous gel, was substantially lower than thin-shelled second-generation implants, despite the longer implantation time.

The Institute of Medicine, in 1999, concluded that quantitative data on rupture incidence over time were lacking for all breast implant types, including third generation implants (Bondurant *et al.*, 1999). Only one study, the Danish MRI study of rupture prevalence by Holmich et al, has employed a valid study design to also detect true rupture incidence (Holmich *et al.*, 2003). Two years after the baseline MRI, the same population of women were examined again with MRI. A true rupture incidence analysis was performed based on 317 implants (in 186 women) that were intact at the baseline MRI (n=280) or were intact at baseline but removed before the second MRI (n=37) (Holmich *et al.*, 2003). The authors observed an overall rupture incidence rate for definite ruptures of 5.2% per year. The rupture rate increased significantly with implant age. For third generation implants (barrier-coated, low bleed implants available since 1988), the rupture-free survival was estimated as 98% at 5 years and 83%-85% at 10 years. Based on these figures, a survival curve was created (Figure 2).

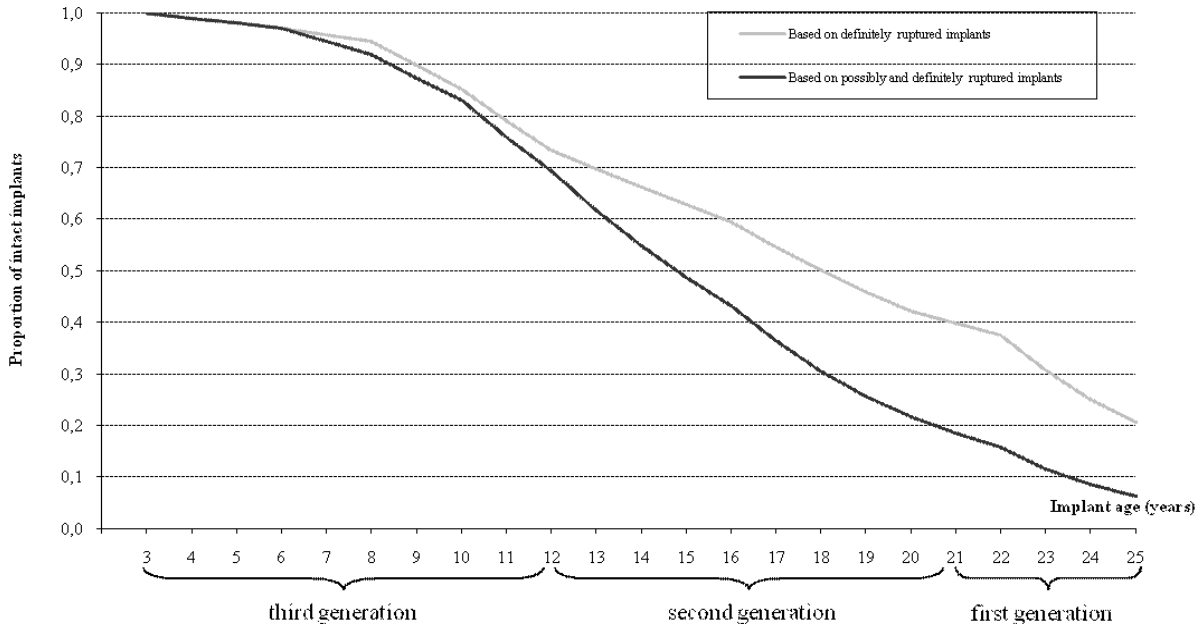

Figure 2: Estimated rupture-free survival curves based on definite ruptures or on definite and possible ruptures combined for all implants implanted at least 3 years before the baseline MRI (Hölmich *et al.*, 2003).

The results of the prevalence and the incidence study concur relatively well. In the prevalence study, 3% of 3–5-year-old third-generation implants and 16% of 6–10-year-old implants were ruptured, while in the incidence study, it was estimated that approximately 2% of third-generation implants would be ruptured by 5 years and 15–17% by 10 years. The third-generation implants were relatively durable for the first 6–8 years, after which the rupture rate increased. The results of previous explantation studies are in line with these studies, indicating that first- and third-generation implants are the most durable, whereas second-generation implants are associated with a much higher frequency of rupture (De Camara *et al.*, 1993, Malata *et al.*, 1994, Robinson *et al.*, 1995, Peters *et al.*, 1997, Cohen *et al.*, 1997, Rohrich *et al.*, 1998 , Feng and Sharpe 1999, Collins *et al.*, 2000).

The overall estimate of implant rupture prevalence in the first Danish study (Hölmich *et al.*, 2001) is somewhat lower than those reported in clinical explantation studies (De Camara *et al.*, 1993, Malata *et al.*, 1994, Robinson *et al.*, 1995, Peters *et al.*, 1997, Cohen *et al.*, 1997, Rohrich *et al.*, 1998 , Feng and Sharpe 1999, Collins *et al.*, 2000). Those studies were, however, based mainly on symptomatic women who elected for surgery, who are likely to have a higher proportion of ruptured implants than unselected women. Moreover, damage to implants during explantation can also lead to an overestimation of *in vivo* failure prevalence (Slavin and Goldwyn, 1995).

6.3.4.3 Third-generation implants

Two reports on implant durability in third-generation implants became public as a result of applications by two implant manufacturers for pre-market approval by the US FDA in 2005 (Heden *et al.* 2006, Collis *et al.* 2007). In a multinational study on Inamed (now Allergan) implants, 8% of 199 implants (both smooth and textured) in 15% of the 106 participating women were diagnosed as ruptured or possibly ruptured at MRI, after a median implantation time of 10.9 years (range, 9.5–13.2 years) (Heden *et al.* 2006). These implants would be categorised as third generation implants. A British study of 149

women with Mentor Siletex gel implants for subglandular breast augmentation was published in 2007 (Collis *et al.* 2007). The same data were included in Mentors pre-market approval (FDA 2006). Eleven percent of implants in 15% of women were diagnosed with rupture at MRI after a mean implantation time of 8.8 years (range, 4.8-13.5 years). At subsequent surgery on a subset of the study population, 29% were false-positives and 4.9% were false-negatives, the rest of implants correctly diagnosed at MRI. The positive predictive value was 61% and the negative predictive value 82%. Using both radiological and explant data, a survival estimate was calculated, showing that by 13 years of implantation, 19% and 12% of Mentor Siltex implants, respectively, will be ruptured. Actually, these figures were seen after 10 years of implantation, but became more precise with larger follow-up. The data from the Allergan and Mentor studies are comparable to the finding in the Danish study, that 7–14% of third-generation implants, with a median age of 6–7 years, were ruptured, depending on the definition of generation (Hölmich *et al.* 2001). The manufacturer-specific rupture prevalences are, however, somewhat better than those in the survival curve from the Danish Rupture incidence study (Hölmich *et al.* 2003) with 17% ruptured implants by 10 years, which is based on several brands of implants.

In the recently published data from 8 and 10 year follow-up on the Core Study patients from Allergan and Mentor breast implants higher cumulative ruptures have been reported. For the Allergan implants, 10-year cumulative MRI diagnosed ruptures were ranging from 6.7 % (95% CI, 2.8-13.7) to 27.2 % (95% CI 17.3-41.3) depending on study group (revision augmentation and primary reconstruction, respectively). For the Mentor implants, 8-year cumulative MRI diagnosed ruptures ranged from 13.6% (95% CI 7.6-23.6) in primary augmentation patients to 21.3% (95% CI 7.3-53.3) in the revision reconstruction group. It is unclear how many of these ruptures have been verified in surgery (FDA 2011).

6.3.4.4 Fourth-generation implants

A few case reports and one large study of the integrity of fourth-generation implants have been published (Shaaban *et al.* 2003, Lahiri and Waters 2006, Heden *et al.* 2006). The case reports demonstrate the ability of cohesive implants to generate extracapsular silicone and enlarged lymph nodes (Shaaban *et al.* 2003, Lahiri and Waters 2006). Heden *et al.* studied 144 women with 286 McGhan/Inamed style 410 implants (maximal cohesive gel), with a median implantation time of 6 years (range, 5–9 years). At MRI examination, one implant (0.3%) was ruptured and two implants (0.7%) had intermediate signs of rupture (Heden *et al.* 2006). Heden *et al.* did a similar study, which was published in 2009, with MRI on 163 women with Allergan style 410 implants; 1.7% were diagnosed as ruptured at MRI after a median implantation time of 8 years (Heden *et al.* 2009). These results indicate that cohesive implants are more durable than the previous generations; however, the silicone membrane of these cohesive implants is identical to that in the third-generation implants of the same manufacturer examined in the study cited above, (Heden *et al.* 2006), and the accuracy of MRI diagnoses of rupture in these implants has not been studied.

6.4 Health effects of silicone breast implants (SBI)

6.4.1 Local effects in the breast

Based on clinical experience, some women with breast implants present with discrete symptoms suspecting to due to an implant rupture. The typical history is a change in the breast configuration, often towards a softer breast, but sometimes as increased

hardness. Both can be indicative of a rupture, as described above. In some cases, a swollen and sore lymph node in the lateral breast or the adjacent axilla is the first clinical sign of an implant rupture. The changes have typically taken place over a few months, but in case of swollen lymph nodes most women seek medical evaluation soon after onset of symptoms (Dowden 1993, Hölmich *et al.*, 2005). Some women have pain in the breast, rarely described as serious, but more like an inner soreness or itching (Hölmich *et al.*, 2005). These symptoms, along with a clinical examination can often give the suspicion of rupture, however, ultrasonography or preferably MRI must be performed in order to verify the diagnosis. In many cases, there may be additional indications for surgery and the imaging part can be left out. In case of an unequivocal clinical examination, a rupture may still be present, and imaging is necessary.

A few studies reported higher frequencies of complaints by women with breast implants ruptures. However, no specific pattern of symptoms was identified (Wells *et al.*, 1994, Hennekens *et al.*, 1996, Englert *et al.*, 2001, Fryzek *et al.*, 2001). A large number of women must have had silent implant rupture at the time of study, based on knowledge from rupture studies.

In order to evaluate breast symptoms as well as more general symptoms in case of untreated implant rupture, a Danish study examined 64 women with 96 implant ruptures which were left untreated over a two-year period (Hölmich *et al.*, 2004). The ruptures were diagnosed at an MRI in 1999, the patients did not have symptoms that warranted explantation at the time of diagnosis and choose to take a "watchful waiting approach". After two years, a new MRI was performed. 11 implants (11%) in 10 women with had progression from intra- into extracapsular rupture (n = 7), as progression of extracapsular silicone (n = 3) or as increasing herniation of the silicone within the fibrous capsule (n = 1). In most cases, these changes were minor. Some of the changes could be ascribed to trauma, but others appeared to be spontaneous. The presence of autoantibodies (Rheumafactor, ANA, Cardiolipin) decreased slightly over time in all women and did not appear to be influenced by implant status. None of the nine women with new or increased extracapsular silicone at the second MRI became seropositive for any of the measured autoantibodies (Hölmich *et al.*, 2004). Women with untreated implant ruptures reported a significant increase in non-specific breast changes (OR, 2.1; 95% CI, 1.2–3.8) when compared with women without ruptures. The changes were primarily a softer breast with a different shape and size and in some cases pain, although not considered serious. The commonest remark was that the breast felt flatter and smaller. Although based on small numbers, there was no excess reporting of new diseases among women with ruptured implants (OR, 0.7; 95% CI, 0.3–1.6). This is the only study to examine untreated ruptures.

Women with extracapsular ruptured implants more frequently reported breast hardness indicative of capsular contracture than women with intact implants. This is consistent with the ability of free silicone to induce a foreign body reaction that can result in fibrosis (Caffee 1986). The fibrous capsule surrounding the implant has been found to act as a natural boundary for silicone, with high levels observed in biopsy samples of capsules and considerably lower concentrations in the breast parenchyma, regardless of implant status (McConnell *et al.* 1997, Peters *et al.* 1996, Schnur *et al.* 1996, Beekman *et al.* 1997). In the study by Beckman *et al.*, there was significantly less silicone migration over the fibrous membrane in women in whom the capsule was calcified and significantly more in patients in whom implantation exceeded 12 years. There was no significant correlation between the status of the implant (intact, bleeding or ruptured) and the degree of silicone migration (Beekman *et al.* 1997). Mechanical stress and trauma, such as manual capsulotomy, have been associated with extracapsular silicone gel leak (Ahn and Shaw 1994, Eisenberg *et al.* 1977, Hölmich *et al.* 2001), but the mechanism of spontaneous migration has not been fully clarified. In the above mentioned Danish study of untreated ruptures intracapsular rupture spontaneously became extracapsular in a few cases (Hölmich *et al.* 2004). This lends further support to the understanding that intracapsular or extracapsular implant rupture is not a permanent condition and that the fibrous

capsule, although solid and sometimes even calcified, is not impermeable to silicone, as seen in both pathological specimens and on MRI.

Some studies have found no association between capsular contracture and implant rupture,(Peters *et al.*, 1994, Collins and Sharpe, 2000) whereas a study of 1619 removed implants found a significant association (OR, 1.52; 95% CI, 1.14–2.03) (Feng and Amini 1999) similar to that in a smaller Danish study (Hölmich *et al.* 2005). All of the reported studies, however, involved symptomatic patients who had undergone explantation, and this might have biased their results. There may be an association between significant capsular contracture and implant rupture, but mutual confounding of both events with increasing implant age makes it difficult to evaluate the true effect. In any case, the association does not appear to be strong.

Women with silicone gel-filled breast implants sometimes develop local and peri-operative complications including serious infections, severe or chronic breast pain, hematoma and the need for additional surgery. Many of these post-operative complications are not unique to breast implantation but occur following various types of surgery in general. Prospective data on the occurrence of local complications following breast augmentation have accumulated in the literature, with several recent reports reporting on the newer generations of implants, although long-term data still remain somewhat limited for these newer highly cohesive implants. There are no epidemiologic data available specifically addressing local complications among recipients of PIP silicone breast implants, however, a review of what is known regarding local complications and cosmetic breast implants in general will provide information and context to this issue.

The reported frequency of local complications among silicone breast implant recipients generally ranges between 17% and 36% (Spear *et al.*, 2007; Cunningham 2007; Hvilsom *et al.*, 2009; Kjoller *et al.*, 2002b; Henriksen *et al.*, 2003, 2005; Fryzek *et al.*, 2001; Kulmala *et al.*, 2004). This variability among studies reflects differences in patients' physical conditions and co-morbidities, implant design, and timing of occurrence of complications. Studies including newer generations of implants and textured implants generally report lower complication frequencies compared with studies of earlier generations of implants. Typically, the most frequent local complication is capsular contracture, with frequencies ranging from 1.9 to 23% in recent reports, while complications such as pain, hematoma, and wound infection are substantially less common and occur during the acute postoperative period, with frequencies generally less than 2%. Additional surgery after primary implantation has been reported as a result of complications in 10 to 30% of implantations. Capsular contracture is the most frequent reason for additional surgery in women with breast implants.

Reports of complications following implantation with the newer generations of implants were published recently by two large implant manufacturers. Spear *et al.* (2007) reported results for 455 women (with 908 Inamed/Allergan implants). During six years of follow-up, the most common local complication was severe capsular contracture (Baker III/IV) which occurred in 15% of the women and was the primary indication for approximately 30% of reoperations. The frequency of capsular contracture is higher in this study compared with others and may be attributed to the fact that only 41% of the implants were textured implants, which have been reported to have a lower incidence of capsular contracture (Collis *et al.* 2000; Wong *et al.*, 2006). Other complications reported after primary augmentation were implant malposition and asymmetry occurring in 5.2% and 3.0% of the women, respectively. Breast pain and swelling occurred among 9.6% and 8.3% of women, respectively, but most often as postoperative complications that resolved within two months after surgery. Twenty-eight percent of the women underwent a reoperation within six years, seven of whom had more than one reoperation.

Cunningham *et al.* (2007) reported results for 551 patients with Mentor implants and three years of follow-up. Severe capsular contracture (Baker III/IV) was the most common complication observed in 8.1% of the women. Fifteen percent of the women

underwent a reoperation within three years, of which 36.7% were due to capsular contracture, 11% to hematoma and 4.6% to asymmetry.

In a multi-site European study of Allergan Style 410 highly cohesive, textured implants (Heden *et al.* 2009), with longer follow-up of 5 to 11 years after implantation, capsular contracture was detected by for 5.3% of implants, consistent with a rate of 5.6% reported in an earlier study by Heden *et al.* (2006) of the same implants. All were grade III capsular contractures. A three-year follow-up study in the United States of 492 women with cosmetic augmentation using the same Style 410 highly cohesive implants (Bengtson *et al.* 2007) reported low complication rates; implant malposition was most common (2.6%), while grade III/IV capsular contracture occurred among 1.9% and other complications, including breast pain, infection or swelling, among less than 2% of women. The risk of reoperation among augmented women was 12.5%, and the primary reasons for reoperation were implant malposition or patient request for size/style change; capsular contracture was the primary reason for reoperation among 6.9% of women in this study.

Cohort studies conducted in Denmark (Hvilsom *et al.*, 2009; Kjoller *et al.*, 2002b; Henriksen *et al.*,2003, 2005), Sweden (Fryzek *et al.*,2001) and Finland (Kulmala *et al.*,2004) have investigated local complications among women with cosmetic breast implants. Hvilsom *et al.* (2010) reported the most recent, long-term prospectively acquired data on local complications from the population-based, prospective Danish Registry for Plastic Surgery of the Breast. The incidence and severity of short-term complications was examined in 5373 women (10 640 implants) who underwent primary cosmetic breast implantation between 1999 and 2007, with a mean follow-up of 3.8 years (range up to 8.7 years); 35% of women had at least 5 years of follow-up. Overall, 97% of the implants were silicone gel filled and 93% had a textured surface. Of the silicone gel-filled, textured implants, 65% were older, less cohesive gel implants, 14% were newer, more cohesive gel implants, and 21% were the newest, very cohesive gel implants. The frequencies of complications among women in this study were generally lower than those reported in other studies, likely due to some underestimation of complications attributable to passive surveillance used by the Registry, as opposed to proactive regular and frequent examinations according to protocol performed in a clinical study. During the entire follow-up period, 16.7% of women developed at least one adverse effect and 4.8% developed a surgery-requiring complication. Within 30 days of implantation, the most common adverse events were infection (1.2%) and hematoma (1.1%), while change of tactile sense (8.7%), asymmetry/displacement of the implant (5.2%) and mild capsular contracture (4.2%) were most common within five years. Less than 1.5% of women reported prolonged pain in the breast within three years or five years following implantation. The frequency of severe capsular contracture (Baker Grade III-IV) was 1.3% within three years and 1.7% within five years after implantation. Displacement or asymmetry (39.9%) and capsular contracture (17.3%) were the most frequent clinical indications for reoperation.

An earlier report from the Danish Implant Registry, based on shorter follow-up, examined determinants of surgery-requiring complications and capsular contracture among 2,277 women who underwent cosmetic breast implantation from 1999 through 2003 (Henriksen *et al.*, 2005). Most implants (76%) contained soft silicone gel (third-generation implants) while 22% contained firm, cohesive gel (fourth-generation implants). During an average follow-up of 119.5 months (range 3-50 months), 12% of implants (17% of women) had short-term complications, of which 136 (3.0%), corresponding to 4.3% of women, required surgical intervention. Capsular contracture grades III through IV was registered among 30 women, 9 of them bilaterally. The most frequent clinical indications for surgical intervention were asymmetry/malposition of implant (38% of surgeries) and capsular contracture grades III to IV (16%). Other less common implant-related complications requiring surgery included periprosthetic infection (1.5%) and breast pain (3.7%). Unsatisfactory cosmetic result was an indication for 51% of the 136 revision procedures.

In their recent clinical practice-based study, Handel *et al.* (2006) reported that the rate of capsular contracture grade III or IV was 1.99 per 1000 patient-months after augmentation and 4.36 per 1000 patient-months after implant revision surgery. The frequency of hematoma and infection ranged between 1.5% and 2.1% following augmentation or revision surgery. For breast augmentation, 248 of 1,601 (15.5%) implants required subsequent reoperation, while 21.9% of implants used for revision surgery required subsequent reoperation. The most common reason for reoperation was capsular contracture (56% of patients requiring additional surgery).

There have been additional recent reports on the occurrence of specific local complications following breast implantation. Fryzek *et al.* (2001) analyzed local complications, based on medical record review, among 1,280 Swedish women with cosmetic breast implants, and found that 69% of the women had no local complications, while 31% had an implant change, implant leakage, or capsulotomy. Fewer complications were reported for women with submuscular implants and for implants having nonsmooth surfaces. The occurrence of local complications was examined among 685 Finnish women with cosmetic breast implants, with a mean follow-up of 10.9 years (range up to 34 years) (Kulmala *et al.*, 2004). Overall, 64% of women had no local complications diagnosed in their medical records. Again, the most common complication was capsular contracture, occurring in 17.7% of women and 15.4% of implants. Wound and skin problems, infection, and hematoma were diagnosed in 2.8%, 2.5%, and 1.8% of women, respectively. Seventy-four percent of women needed no postoperative treatment, while 22% required surgery after primary implantation. Breiting *et al.* (2004) conducted a study of 190 Danish women with long-term cosmetic silicone breast implants compared with 186 women who had undergone breast reduction surgery. Eighteen percent of women with implants self-reported chronic breast pain, compared with 8% among women with breast reduction. Pittet *et al.* (2005) reported that the rate of infection after silicone gel-filled breast implantation is 2-2.5%, and that two-thirds of infections occur within the acute postoperative period. The risk of infection was higher in women who had breast reconstruction after mastectomy and radiotherapy for cancer than in augmentation patients.

Thus, the epidemiologic evidence demonstrates that the incidence of short- and long-term local complications following silicone gel breast implantation is relatively low and does not typically require additional surgery. Capsular contracture is the most frequently reported complication and the most frequent cause of surgical intervention, while the frequencies of other complications such as breast pain, infection, and malposition are much lower, often as low as 1-2%. Long-term data on the newest generation of textured, highly cohesive gel implants are somewhat limited, although results from follow-up up to 11 years is consistent with a low rate of local complications.

6.4.2 Lymphoma

Concerns about non-Hodgkin lymphoma (NHL) among women with breast implants have been raised by anecdotal reports of lymphomas in or near the breast among women with breast implants (Brody *et al.*, 2010; Newman *et al.*, 2006; Gaudet *et al.*, 2002; Sahoo *et al.*, 2003; Keech and Creech 1997; Duvic *et al.*, 1995). A pooled analysis of NHL incidence in five long-term cohort studies with virtually complete follow-up of 43,537 women with cosmetic breast implants in Denmark and Sweden, the US, Canada, and Finland yielded a SIR of 0.89 (95% CI 0.67-1.18), based on 48 observed NHL cases (Lipworth *et al.*, 2009). None of the studies reported a primary lymphoma of the breast. Thus, the epidemiologic evidence, based on large surveillance studies with long-term follow-up, does not provide evidence of an increased risk of NHL of any site among women with cosmetic breast implants. In the only published cancer incidence study to include women followed for at least 25 years after implantation (Lipworth *et al.*, 2008), including 3,336 women followed for 15 years or more and 827 followed for at least 25 years, no significant excess of NHL was observed overall and not one primary lymphoma of the breast was observed. Moreover, the largest study to date (Brisson *et al.*, 2006),

with cancer surveillance as long as 24 years, actually reported a reduced incidence of NHL among almost 25 000 Canadian women with cosmetic breast implants.

Recently, a report of a case-control study from the Netherlands suggested an association of breast implants with anaplastic large cell lymphoma (ALCL) (De Jong *et al.*, 2008), although the latency period between placement of the implants and ALCL diagnosis was remarkably short (< five years) for three of the five ALCLs diagnosed in implant women, weakening the plausibility that any observed association with implants is causal in nature. All the cases in this study were reported to be patients with ALCL of the breast identified in the Netherlands between 1990 and 2006, while all of the controls had lymphomas of the breast but of cell types other than ALCL diagnosed during the same time period. Thus, the elevated odds ratio presented in the paper does not demonstrate an increased risk of ALCL of the breast among augmented women per se. In fact, no valid conclusion at all can be drawn regarding whether there is an excess of lymphoma overall, or of ALCL in particular, among women with breast implants compared with women without implants, since control patient selection purposefully comprised only patients with breast lymphomas other than ALCL. Of interest, all five of the women with ALCL and breast implants had bilateral "saline-filled" implants, which are used infrequently in Northern Europe, where silicone breast implants have not been taken off the market as they were in North America. Thus, the only valid conclusion that can be drawn from this study is that among women with breast lymphomas in the Netherlands, those whose pathology is of the anaplastic, large cell type variety may be more likely to have received saline implants (Lipworth *et al.*, 2009).

Lymphomas of the breast are rare, comprising 0.04-0.5% of all breast cancers (Kim *et al.*, 2011a, 2011b), and the vast majority of are B-cell origin. Anaplastic large cell lymphoma is a rare type of lymphoma, or cancer of the immune system, characterized by abnormal growth of T-lymphocytes that occurs in several parts of the body, including lymph nodes, skin (cutaneous ALCL), breast, bones or soft tissue. ALCL is not cancer of the breast tissue. Rather, implant-associated ALCL falls within a broad spectrum of lymphoproliferative disorders with variable clinical behaviors, raising questions about a diagnosis of malignancy in many instances (Jewell *et al.*, 2011). According to the United States National Cancer Institute, approximately 1 in 500,000 women is diagnosed with ALCL in the United States each year, with ALCL in the breast even less common, diagnosed in 3 in 100 million women per year (FDA, 2011). In 2011, an FDA summary of the literature through May 2010 identified at least 34 unique cases of ALCL among women with breast implants, and concluded that women with breast implants may have a very small but increased risk of developing ALCL in the scar capsule adjacent to the implant (FDA 2011). Of the 34 cases, the median time from breast implantation to ALCL diagnosis was 8 years (range 1-23 years), and ALCL in women with breast implants is generally located in the region immediately surrounding the breast implant (seroma or fibrous capsule) but without invasion of the breast parenchyma. Most ALCL patients were diagnosed at the time of medical treatment for complications such as persistent seromas, capsular contracture or peri-implant masses. The evidence on implant characteristics, in particular implant surface, is too limited to evaluate whether implants with textured or smooth outer shell are associated with ALCL. As stated by the FDA, "the totality of the evidence continues to support a reasonable assurance that FDA-approved breast implants are safe and effective when used as labeled."

Several independent reviews of the literature pertaining to ALCLs among women with breast implants have been published (Kim *et al.* 2011b; Jewell et al, 2011; Brody *et al.* 2010). In a review of 36 clinical cases of NHLs involving the breast among women with implants, 29 were ALCLs (Kim *et al.*, 2011b). However, 12 of the 29 women with ALCLs had a prior history of cancer other than T-cell lymphoma and two had a prior history of T-cell lymphoma. Similarly, Brody *et al.* (2010) identified 34 cases of T-cell ALCL among women with breast implants, all presenting as late peri-implant seromas, capsular contracture or peri-capsular tumor masses. The authors obtained preliminary data on brand and style of implant for 25 of the cases, and reported that 23 of them had a

specific textured surface created by the lost salt method. Most if not all of these cases likely overlap with those reviewed by the FDA.

In summary, a potential association between ALCL and breast implants in general, or implants with particular characteristics such as a textured shell in particular, has been suggested by anecdotal reports of small numbers of women. A causal link between breast implants has not been established, nor has an association been evaluated in a large, well-designed epidemiologic study to date.

6.4.3 Other forms of cancer

More than a dozen epidemiologic studies, many of which have been large and able to assess long-term risks, have been conducted in North America and Europe to evaluate the potential association between cosmetic breast implants and the incidence of breast and other cancers (Breiting *et al.*, 2004; Gabriel *et al.*, 1994; Brinton *et al.*, 1996,2000a,2001a; Bryant and Brasher, 1995; Deapen *et al.*, 1997; Kern *et al.*, 1997; Malone *et al.*, 1992; Park *et al.*, 1998; McLaughlin *et al.*, 1998,2006; Mellemkjaer *et al.*, 2000; Pukkala *et al.*, 2002; Friis *et al.*, 2006; Brisson *et al.*, 2006; Lipworth *et al.*, 2008). There are no data available specifically on the incidence of cancer among recipients of PIP silicone breast implants.

The primary concern among breast implant patients, the medical community, and regulatory agencies was breast cancer risk because of the location of the implants, their use for reconstruction following breast cancer, and the hypothesis that they may interfere with mammographic detection of breast cancer. Some early reports also raised concern that women with silicone gel-filled breast implants may be at increased risk of developing other cancers, including lung cancer, cancers of the cervix and vulva, leukemia, and multiple myeloma. However, epidemiologic studies have been remarkably consistent in finding no evidence of increased breast cancer risk among women with breast implants, and the weight of the epidemiologic evidence is consistent with there being no causal association between breast implants and any other type of cancer. Accordingly, independent scientific reviews have unanimously concluded that there is no demonstrated excess of cancer of any type among women with silicone breast implants (Bondurant *et al.*, 1999; McLaughlin *et al.*, 2007; EQUAM, 2000; International Agency for Research on Cancer, 1999; National Institutes of Health, 2005). Indeed, in 1999, the International Agency for Research on Cancer (IARC) took the unusual step of concluding that there was evidence of a lack of breast carcinogenicity in women with silicone breast implants, and this conclusion was supported by that of the independent report of the IOM Committee on the Safety of Silicone Breast Implants (Bondurant *et al.*, 1999).

Numerous epidemiological studies have continued to evaluate risk of breast and other cancers in women with silicone gel-filled breast implants. In a pooled analysis of the two large Scandinavian, nationwide cohort studies with virtually complete follow-up and cancer ascertainment (Lipworth *et al.*, 2008), 3486 Swedish women (McLaughlin *et al.*, 2006) and 2736 Danish women (Friis *et al.*, 2006) who received cosmetic implants between 1965 and 1993 were followed for up to 37 years, with more than half followed for 15 years or more. There was no statistically significant increase in cancer incidence overall, compared with the general population of age-matched women. Similarly, Pukkala *et al.* (2002) conducted a cohort study of 2171 Finnish women with cosmetic breast implants, with a mean length of follow-up of 8.3 years. Cancer incidence overall was similar to that expected in the general population. Brinton *et al.* (1996,2000a) conducted a retrospective cohort study of the incidence and mortality of cancers of various types among 13 488 women with silicone breast implants compared with 3936 women who had other types of plastic surgery as well as with women in the general population. There was a slight excess of cancer incidence overall among women with implants (SIR=1.2; 95% CI 1.1-1.4) when compared with women in the general population, but not when compared with other plastic surgery patients (Brinton *et al.*, 2000a). In the large Canadian cohort study, the incidence rate for cancer at all sites combined was significantly reduced among 24 558 women with implants compared with

the general population (SIR=0.75; 95% CI 0.70-0.81) and was similar to that among other plastic surgery patients (Brisson *et al.*, 2006).

The incidence of breast cancer was below expectation in virtually all the large-scale epidemiologic studies, with risk ratios suggesting a reduction of 10-50%. In the pooled Scandinavian study (Lipworth *et al.* 2008), there was a significantly reduced incidence of breast cancer among women with implants, with 84 cases observed compared with 115.62 expected (SIR=0.73; 95% CI 0.58-0.90). The combined mean duration of follow-up among all women with implants was 16.6 years (range 0.1-37.8 years). Over 50% (n=3,280) of women in the cohort were followed for 15 years or more after implantation, and 13.2% (n=824) were followed for at least 25 years. When the SIR for breast cancer was evaluated stratified by time since breast implantation, breast cancer SIRs were non-significantly reduced throughout the follow-up period. The corresponding SIR for breast cancer in the large Canadian study was 0.57 among 24,558 women with implants (Brisson et al, 2006). The consistently observed reduced incidence of breast cancer among women with breast implants may be explained by a higher prevalence of patient characteristics which may put them at a lower risk for breast cancer, including younger age at first birth, higher parity and lower body mass index (Kjoller et al, 2003; Cook et al, 1997; Fryzek et al, 2000; Brinton et al, 2000b). Most studies of cancer among women with breast implants did not have information on reproductive characteristics of the particular women included in the study. However, in a separate analysis of the Danish women with implants included in the pooled Scandinavian study, the reduction in breast cancer risk persisted even after adjustment for age at first birth and number of children (Friis et al, 2006), suggesting that reproductive factors may not have a major influence. It is also plausible that women seeking cosmetic breast implantation may be diagnosed with breast cancer during preoperative screening. Exclusion of these women whose breast cancers would have ultimately been diagnosed during follow-up could lead to decreased incidence of breast cancer among women with cosmetic breast implants compared with women in the general population, although these effects are unlikely to explain the persistent risk reduction with long-term follow-up.

The IOM (Bondurant *et al.*, 1999) suggested that implants may make screening mammography more challenging by obscuring a variable part of breast tissue. Based on the findings of a few case series (Fajardo *et al.*, 1995; Silverstein *et al.*, 1988, 1990, 1992), many originating from the same clinic, a hypothesis was generated that opaque breast implants may interfere with physical breast examination or mammographic visualization of breast tumors, leading to delays in breast cancer diagnosis and worse prognosis among women receiving implants. However, the interpretation of these clinical case series is hampered by potential referral or ascertainment bias, small sample size and absence of a control group. Furthermore, many of the women included in these case series underwent their mammograms prior to the implementation of Eklund's implant displacement technique which improved the accuracy of mammograms for women with breast implants (Eklund *et al.*, 1988), although a portion of the breast may still not be adequately visualized.

Numerous epidemiologic studies have evaluated whether implants delay the detection of breast cancer by comparing the stage distribution among women with implants at breast cancer diagnosis with an appropriate comparison group. Virtually all of these studies indicate that, although the sensitivity of mammography may be reduced somewhat in women with breast implants, these women do not in fact present with more advanced stages of breast cancer or suffer from reduced survival after breast cancer diagnosis (Friis *et al.*, 2006; McLaughlin *et al.*, 2006; Deapen *et al.*, 2000; Hoshaw *et al.*, 2001; Miglioretti *et al.*, 2004; Holmich *et al.*, 2003c). Most recently, Xie *et al.* (2010) reported on stage distribution and prognosis among 182 and 202 incident cases of breast cancer identified in the large Canadian cohorts of women with breast implants and women with other plastic surgery procedures. Women with breast implants were more likely to be diagnosed with a more advanced stage of breast cancer compared with other plastic surgery patients; however, there were no differences in tumor size and breast cancer-

specific survival was similar in both groups. Moreover, none of the mortality studies to date has demonstrated an increased risk for death from breast cancer among women with implants compared with women in the general population (Lipworth *et al.*, 2007; Jacobsen *et al.*, 2004; Brinton *et al.*, 2006; Villeneuve *et al.*, 2006).

Few statistically significantly increased or decreased SIRs were observed for other types of cancers in any of the studies. A significant increase in lung cancer (SIR=2.2; 95% CI 1.3-3.4) was observed among women with implants in the Swedish study (McLaughlin *et al.*, 2006). An earlier survey based on a randomly selected subset of these Swedish women with breast implants found that they were 2.8 times more likely to be current smokers than the general population of Swedish women (Fryzek *et al.*, 2000). This difference in smoking habits is likely to explain the increase in lung cancer risk among women in this study, as well as the excess of lung cancer mortality among women with breast implants in a Swedish mortality study (Lipworth *et al.*, 2007). The slight excess of total cancer in the study by Brinton *et al.* (2000a) was due primarily to statistically significant increased risks of cervical, vulvar, and brain cancer, and leukemia compared with the general population. Substantial differences in demographic, lifestyle, and/or reproductive characteristics between women with implants and both women with other types of cosmetic surgery and women in the general population have been reported in several epidemiologic studies (Fryzek *et al.*, 2000; Kjoller *et al.*, 2003; Cook *et al.*, 1997; Brinton *et al.*, 2000b) and are likely to account for these sporadic excesses of cancer, in particular vulvar, cervical and lung cancer.

Brain cancer has been studied quite extensively in several large-scale incidence studies (Pukkala *et al.*, 2002; Friis *et al.*, 2006; McLaughlin *et al.*, 2006; Brisson *et al.*, 2006; McLaughlin and Lipworth, 2004), as well as in five mortality studies (Lipworth *et al.*, 2007; Jacobsen *et al.*, 2004; Brinton *et al.*, 2001b,2006; Pukkala *et al.*, 2003; Villeneuve *et al.*, 2006), all of which consistently failed to demonstrate any significant excess among women with cosmetic breast implants. Only one study to date has reported a significant excess of brain cancer among women with breast implants (Brinton *et al.*, 2001b), but upon further follow-up no additional deaths from brain cancer were observed (Brinton *et al.*, 2006), yielding a non-significant standardized mortality ratio (SMR) of 1.4 (95% CI 0.8-2.5) after an average of 20 years of follow-up.

In summary, the results of the most recent investigations are remarkably consistent with earlier epidemiologic evidence in demonstrating no credible evidence of a causal association between breast implants and any type of cancer, including cancer of the breast.

6.4.4 Other effects

Rupture of silicone breast implants has anecdotally been associated with severe symptoms. Subsequent to trauma or closed capsulotomy, episodes of transcutaneous or intraductal extension of silicone from a ruptured implant have been described, (Ahn and Shaw 1994, Leibman *et al.*, 1992) as has distant migration of free silicone via facial planes (Huang *et al.*, 1978, Teuber *et al.*, 1999) and alarming growth in silicone granulomas, probably representing rare runaway foreign body reactions, resulting in devastating tissue excisions(Teuber *et al.*, 1999, Malyon *et al.*, 2001). Such events are rare, although most clinicians with several years in practice have knowledge of a case or two. No studies have quantified the frequency of occurrence of these events.

To date, only one prospective study has addressed the possible health implications of ruptured, *in situ* silicone breast implants. In this unique study, Holmich and colleagues (2004) examined the possible health implications, including changes over time in MRI findings, serological markers, or self-reported breast symptoms, of untreated silicone breast implant ruptures. Sixty-four women with implant rupture diagnosed by MRI were followed for two years, and a second MRI was performed. A control group of women with no evidence of rupture on either MRI was used for comparison. The majority of women had no visible MRI changes of their ruptured implants. Progression of silicone leakage (either herniation of silicone within the fibrous capsule, migration from the intracapsular

space into the surrounding tissue, or progression of extracapsular silicone) was observed in 11 implants (11%) in ten women; in most cases the changes were small. There was no increase in autoantibody levels, and no increase in reported breast hardness among these women. They did report a significant increase in non-specific breast changes compared with women in the control group. The authors concluded that, for most women, rupture is a harmless condition which does not appear to progress or to produce significant clinical symptoms. Based on their findings, they concluded that routine explantation in asymptomatic women with ruptures may not be mandatory. They recommend that asymptomatic women with implant ruptures be followed regularly by clinical examination and that the women should be informed of signs of silicone migration and in that situation explantation should be adviced. (Holmich *et al.*, 2004).

It has been hypothesized that women with ruptured implants may experience increased exposure to silicone, which in turn could induce an immunological reaction leading to a higher risk of specific symptoms or systemic diseases (Press *et al.*, 1992; Melmed, 1998; Solomon, 1994). As previously reviewed by Holmich *et al.* (2007), only two studies of either CTDs or related symptoms evaluated by implant rupture status were based on patients not thought to be selected by the clinical course or symptoms.

In the magnetic resonance imaging (MRI) study by Brown *et al.* (2001), 236 (68.6%) of 344 women from two volunteer plastic surgery clinics had at least one ruptured implant; 73 of these 236 women had an extracapsular rupture. Women with breast implant rupture (overall or extracapsular rupture) were no more likely than women with intact implants to self- report a diagnosis of any of the definite CTDs studied, including fibromyalgia, or symptoms including joint symptoms, skin rash, cognitive disorder, fatigue, or hair loss. When women with extracapsular silicone were compared with a combined group of women with intracapsular rupture and women with intact implants, excesses were found for self-reported Raynaud's syndrome (OR=4.2; 95% CI 1.1-16.0) and fibromyalgia (OR=2.8; 95% CI 1.2-6.3). However, there is no biologic or scientific rationale for comparing women with extracapsular rupture with a combined group of women with intracapsular rupture and women with intact implants, since women with intracapsular rupture had fibromyalgia rates substantially lower (8%) than women with intact implants (14.8%). If the analyses had been conducted appropriately, based on three separate categories of implant status (intact, intracapsular rupture, extracapsular rupture), the fibromyalgia OR for extracapsular rupture compared with intact implants would be 1.9 (95% CI 0.8-4.3), substantially lower than the 2.8 reported by the authors (Lipworth *et al.*, 2004a). Moreover, the study had considerable potential for selection bias due to recruitment procedures and low response rates, and could not determine whether self-reported conditions occurred before or after breast augmentation (Lipworth et al., 2004a).

In a sample of women from the Danish implant cohort who were randomly selected to undergo MRI to detect rupture, Holmich et al. (2003b) evaluated risk of CTD by rupture status among 238 women with cosmetic silicone breast implants. Ninety-two (39%) of the women had MRI-diagnosed ruptures, of which 69 were intracapsular and 23 were extracapsular, and 146 had intact implants. One year prior to the MRI, information was obtained on self-reported CTDs and symptoms with onset after breast augmentation. Two women in the ruptured group (both with extracapsular ruptured implants) and three women with intact implants self-reported a diagnosis of definite CTD, yielding ORs of 0.9 (95% CI 0.1-6.7) for women with ruptured implants overall and 3.8 (95% CI 0.4-35.1) for women with extracapsular ruptures compared with women with intact implants. For undefined CTD or other chronic inflammatory conditions, including fibromyalgia, the corresponding ORs were 1.0 (95% CI 0.3-3.0) and 0.8 (95% CI 0.1-4.5), respectively. Two cases of fibromyalgia were reported, one in the group with intact implants (0.7%) and one in the group with intracapsular rupture (1.4%). None of the women with extracapsular rupture reported fibromyalgia. These rates of fibromyalgia are consistent with the estimated prevalence rate of 3.4% for US women (Wolfe *et al.*, 1995), as opposed to the much higher rates of fibromyalgia reported among women with intact

implants or intracapsular ruptures in the study by Brown *et al.* (2001), again suggesting biased selection of women in that study.

6.4.5 Connective Tissue Disorders (CTD)

6.4.5.1 General aspects

Initially, the primary concern regarding breast implants was the occurrence of systemic sclerosis and other connective tissue diseases (CTDs), including systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögren's syndrome, and fibromyalgia. It had also been hypothesized that women with breast implants experience symptoms of apparent connective tissue, rheumatic, or autoimmune origin that bear some resemblance to fibromyalgia but do not fulfill established diagnostic criteria for any known CTD, including cognitive dysfunction, severe joint and muscle pain, incapacitating fatigue, and skin abnormalities (Kallenberg, 1994; Wolfe, 1999). Although unsubstantiated claims still appear from time to time regarding an association between silicone breast implants and known or atypical CTDs, these have been unequivocally refuted by the reassuringly consistent epidemiologic evidence from published large-scale cohort (Breiting *et al.*, 2004; Brinton *et al.*, 2004; Brown *et al.*, 2001; Edworthy *et al.*, 1998; Englert *et al.*, 2001; Friis *et al.*, 1997; Fryzek *et al.*, 2007; Gabriel *et al.*, 1994; Giltay *et al.*, 1994; Hennekens *et al.*, 1996; Holmich *et al.*, 2003b; Kjoller *et al.*, 2001; Lee *et al.*, 2010; Nyren *et al.*, 1998a; Park *et al.*, 1998a; Sanchez-Guerrero *et al.*, 1995; Schusterman *et al.*, 1993; Wells *et al.*, 1994) and case-control (Burns *et al.*, 1996; Dugowson *et al.*, 1992; Englert *et al.*, 1996; Goldman *et al.*, 1995; Hochberg *et al.*, 1996; Lai *et al.*, 2000; Laing *et al.*, 1996, 2001; Strom *et al.*, 1994; Williams *et al.*, 1997; Wolfe and Anderson, 1999) studies, as well as numerous meta-analyses and critical qualitative reviews (Bondurant *et al.*, 1999; Blackburn and Everson, 1997; Hochberg and Perlmutter, 1996; Independent Review Group, 1998; Janowsky *et al.*, 2000; Lamm, 1998; Lewin and Miller, 1997; Lipworth *et al.*, 2004a,2004b,2010a; McLaughlin *et al.*, 2007; Silman and Hochberg, 2001; Silverman *et al.*, 1996; Tugwell *et al.*, 2001). Among these qualitative reviews is the US Federal court-appointed National Science Panel Report in 2001 (Tugwell *et al.*, 2001), as well as other more recent reviews (Lipworth *et al.*, 2004a,2004b,2010a; McLaughlin *et al.*, 2007) of findings from epidemiologic studies published after the National Science Panel's review, all of which have concluded that there is no credible evidence of an association between breast implants and any of the traditional CTDs evaluated individually or in combination, or atypical CTD.

6.4.5.2 Established connective tissue disease

In an early, large, well-designed epidemiologic cohort study of US female health professionals, evidence initially suggestive of a relation between well-defined CTDs and breast implants was reported (Hennekens *et al.*, 1996; Lee *et al.*, 2010). In the first analysis, there was a small but significant overall increased risk of self-reported (not validated) CTDs among women with breast implants (Hennekens *et al.*, 1996). Due to the self-reported nature of the CTD result, a subsequent medical record validation of these data was performed by the same investigators, showing clear evidence of over-reporting of CTD by the participants, as only 22.7% of self-reported cases of definite CTD could be confirmed by a review of patient records (Karlson *et al.*, 1999). In the latest update from the same study population (Lee *et al.*, 2010), initially statistically significantly elevated relative risks (RR) of 1.6-1.8 for self-reported CTDs or for CTDs ascertained using a specialized CTD screening questionnaire (CSQ) were again found to be greatly attenuated and no longer significant when the analysis was restricted to CTD cases confirmed by medical records. Among women with implants, CTD diagnoses were confirmed for only 27% of women who screened positive for CTD on the CSQ, and for 18% of women who self-reported a CTD. The most informative result of this study, therefore, is the high level of CTD over-reporting by women with implants, particularly among US women with implants when there was nationwide litigation, sensational media

reports, and a government de facto ban of the use of silicone-filled cosmetic breast implants. For most other industrialized countries, this was not the environment.

Over-reporting was similarly evident in a US cohort study (Brinton *et al.*, 2004) of 7234 women with breast implants, in which only a small minority of self-reports of rheumatoid arthritis, scleroderma and Sjogren's syndrome were considered "likely" (i.e., likely real) after medical record review by a panel of expert rheumatologists. For the remainder, the diagnoses were not supported, either because records were incomplete or because clinical criteria were not met. Based on these "likely" diagnoses, RRs among women with implants were non-significantly elevated for the three disorders combined (RR=2.5; 95% CI 0.8-7.8) or for rheumatoid arthritis alone (RR=1.9; 95% CI 0.6-6.2). The US study also found that women with breast implants were not more likely to have fibromyalgia than women with other types of plastic surgery, based on self-reports (RR=1.3; 95% CI 0.9-1.7).

In a study of Danish women (Breiting *et al.*, 2004) with long-term follow-up up to 35 years after implantation, no significant association for all CTDs combined was reported among 190 women with cosmetic silicone breast implants when compared with either 186 breast reduction controls (RR=0.8) or 149 women in the general population (RR=1.4). This study was able to identify women who had received their implants on average almost two decades earlier, but due to the relatively small sample size had limited statistical power to observe associations with rare outcomes such as individual CTDs.

Fryzek *et al.* (2007) reported on the occurrence of CTD in an extended follow-up of an earlier study of 2761 Danish women with breast implants and 8807 comparison women who underwent breast reduction surgery (Kjoller *et al.*, 2001). The women with implants were followed with virtually complete follow-up for an average of 13.4 years, and all CTD outcomes were based on hospital records and were medically verified through medical chart review to evaluate possible misclassification of these diseases at discharge in the study cohorts. Over 85% of CTDs diagnosed in hospital records were confirmed through medical chart review for women with breast implants. Compared with either general population rates or with women with breast reduction, women in the implant cohort had no significant increase in the incidence of combined CTDs or of any specific CTD, including rheumatoid arthritis, dermato- and polymyositis, systemic sclerosis, SLE, and Sjögren's syndrome. Direct comparison of the implant and comparison cohorts showed no relation for breast implants with confirmed fibromyalgia.

Nyren *et al.* (1998a) conducted a large Swedish cohort study that included 3500 women with cosmetic breast implants, followed for a mean of 10.3 years, and 3353 women with breast reduction followed for a mean of 9.9 years. This study relied on a medical record data review to correct for all misclassified and pre-existing (prevalent) CTD diagnoses in both cohorts. In a direct comparison with women who had undergone breast reduction, the RR for hospitalization for total CTDs was 0.8, and no significant increases were found among women with breast implants for any specific CTD, including rheumatoid arthritis, SLE, Sjogren's, or scleroderma. The RR for fibromyalgia among women with breast implants was 1.0 (95% CI 0.3-3.0) compared with women who had undergone breast reduction.

Englert *et al.* (2001) conducted a retrospective cohort study in Australia of 458 women who received cosmetic breast implants between 1979 and 1983 and 687 women with other types of plastic surgery. Diagnoses of CTDs subsequent to implantation or other plastic surgery were self-reported and then validated through medical record review. There was no statistically significant difference between women with breast implants and controls in the reporting of any CTD or of systemic sclerosis, SLE, or rheumatoid arthritis.

With respect to fibromyalgia, a case-control study by Wolfe and Anderson (1999) found no association between silicone breast implants and the subsequent development of fibromyalgia. Utilizing a longitudinal clinical databank of patients seen at a rheumatic disease clinic from 1991 through 1994, history of breast implantation (including date of

implantation) was ascertained among 508 women with fibromyalgia, as well as among 464 women with rheumatoid arthritis and 261 rheumatic disease controls with osteoarthritis. The fibromyalgia patients were the least likely to have had breast implantation prior to their diagnosis. When women with fibromyalgia were compared with women with osteoarthritis, who were selected by the investigators to serve as the relevant disease control group, the odds ratio (OR) for fibromyalgia diagnosed after implantation was 0.77 (95% CI 0.13-4.65), highlighting the importance of determining, in studies of breast implants, whether self-reported CTDs or symptoms occurred before or after breast augmentation surgery.

Similarly, Lai *et al.* (2000) conducted a case-control study of women seen at a rheumatology practice in Atlanta from 1986 through 1992 to ascertain prior history of breast implantation and fibromyalgia. Medical records were reviewed for 2500 women, of whom 131 had a history of breast implantation and 484 met the American College of Rheumatology criteria for fibromyalgia. There was no association between breast implantation and fibromyalgia.

In addition to the studies reported above, a number of earlier cohort studies, most with shorter follow-up and fewer study subjects, also found no increased risk of definite CTDs among women with cosmetic breast implants when compared with either women who had undergone breast reduction or women in the general population, although the relatively small numbers of rare outcomes such as specific CTDs reported in these studies often precluded meaningful comparisons. Included among these early studies are the "Mayo Clinic Study" of 749 women in Minnesota, who received silicone breast implants between 1964 and 1991 and were followed for an average of 7.8 years (Gabriel *et al.*, 1994); a study of 1183 women with breast implants identified from the Harvard Nurses' Health Study cohort (Sanchez-Guerrero *et al.*, 1995); and a nationwide Danish Hospital Discharge Register study (Friis *et al.*, 1997) of 1135 women with cosmetic breast implants.

6.4.5.3 "Atypical" connective tissue disease

Studies that evaluated undifferentiated or atypical CTD as an outcome, defined as having a case definition distinct from the other established CTDs and substantive symptoms (Williams *et al.*, 1997), have consistently reported no credible evidence of an association with silicone breast implants or of a rheumatic symptom profile unique to these women and/or indicative of a specific atypical CTD (Bondurant *et al.*, 1999; Breiting *et al.*, 2004; Brinton *et al.*, 2004; Fryzek *et al.*, 2001a, 2007; Jensen *et al.*,2001a, 2001b; Kjoller *et al.*, 2001; Laing *et al.*, 2001; Lipworth *et al.*, 2004b, 2010a; Tugwell *et al.*,2001).

In the Danish follow-up study (Fryzek *et al.*, 2007), unspecified rheumatism (which included fibromyalgia and myalgia) was statistically significantly elevated in both the implant cohort (standardized incidence ratio (SIR)=1.9; 95% CI 1.6-2.2) and in the comparison cohort of 8,807 women who underwent breast reduction surgery (SIR=1.5; 95% CI 1.4-1.7) cohorts, when compared with the general population. A validation of the diagnosis "unspecified rheumatism" (Jensen *et al.*, 2001b) did not reveal a rheumatic symptom profile unique to women with silicone breast implants or suggestive of atypical CTD. Jensen *et al.* (2001a) examined rheumatic diagnoses and related symptoms among women with implants with and without a prior diagnosis of muscular rheumatism, and observed that the frequency of fibromyalgia and the number of tender points were markedly increased among women with earlier muscular rheumatism compared with women without a prior diagnosis of muscular rheumatism. These results, again, indicate the importance of taking prior rheumatic complaints and diseases into consideration when evaluating current rheumatic diseases among women with breast implants.

In the US study of CTDs by Brinton *et al.* (2004), the authors included a category of self-reported conditions termed "other disorders." The RR for these self-reported disorders among women with implants compared with other plastic surgery controls was 1.4 (95% CI 0.8-2.6) for the period before 1992 and 3.6 (95% CI 1.9-7.0) for the period after 1992, during which breast implant litigation and media reports were widespread in the

United States, suggesting strong reporting bias inherent in these self-reports of CTDs during a period of widespread litigation and publicity. Moreover, the authors indicate that most of these "other CTDs" were "vaguely defined or should not have been considered CTDs."

In the largest study to date to examine symptom reporting for a pattern unique among breast implant recipients (Fryzek *et al.*, 2001a), 1546 Swedish implant patients and 2496 breast reduction controls completed a questionnaire regarding rheumatologic and other symptoms. Women with breast implants reported a multitude of symptoms, but with a clear lack of specificity. Thus, after extensive cluster analysis, there was no identifiable cluster of symptoms indicative of a specific "atypical" CTD, nor was there a unique pattern of inflammatory rheumatic disorders or soft-tissue complaints among women with silicone breast implants.

6.4.6 Offspring effects

There are no epidemiologic data available on offspring effects among women with PIP silicone breast implants. However, there have been several well-conducted, long-term studies of offspring effects among women with implants dating back to the 1990's.

There were isolated early case reports of children born to or breastfed by women with silicone breast implants who developed swallowing difficulties, irritability, nonspecific skin rashes, fatigue, and other symptoms (Gedalia *et al.*, 1995; Levine and Ilowite, 1994; Levine *et al.*, 1996a,1996b,1996c; Teuber and Gershwin, 1994). Besides the lack of a control group in these case series or small clinical studies, selection bias is a major concern due to the referral of children to a gastroenterology clinic because of a concern about breast implants, including those whose mothers were involved in implant litigation (Bartel, 1994; Cook, 1994; Epstein, 1994; Placik, 1994). In addition, some of the children were born to families with a history of scleroderma and esophageal dysmobility, so genetic or familial factors cannot be ruled out, and sedation of the children during testing may have affected oesophageal pressures.

Four population-based retrospective cohort studies have examined health outcomes among children born to mothers with silicone breast implants, and none has found evidence of such a relationship.

Kjoller *et al.* (1998) examined the occurrence of oesophageal disorders, connective tissue diseases (CTD), and congenital malformations among 399 Danish children of mothers who received breast implants at public hospitals between 1977 and 1992, compared with 3906 children of mothers who had undergone breast reduction. After a mean follow-up of 5.5 years (range up to 15.7 years), higher than expected rates of oesophageal disorders were found among children born to mothers with implants, compared with the general population; however, similar excesses were observed among the control group of offspring born to mothers with breast reduction surgery, and excesses were also observed among children born prior to the mother's implant surgery. The observation of an increased occurrence of oesophageal disorders among the offspring of women with implants both before and after implant surgery, and women with breast reduction suggests confounding by some characteristics of women who undergo cosmetic breast operations in general as a likely explanation for the observed excesses. There were no significant increases in CTD or congenital malformations in either the breast implant or breast reduction cohorts.

Kjoller *et al.* (2002a) reported on an additional cohort of children of Danish women who received implants at private plastic surgery clinics between 1973 and 1995, and updated the follow-up of the earlier public hospital implant and reduction cohorts (Kjoller *et al.*, 1998). The mean follow-up after breast implantation for the private clinic and public hospital cohorts combined was 6.0 years (range up to 19 years). Esophageal disorders, rheumatic disease, and congenital malformations were examined among 2854 children born to Danish women with implants and 5805 children born to women who underwent breast reduction or other plastic surgery. Significantly higher than expected rates of

esophageal disorders were observed for children born before (SIR=2.0; 95% CI 1.3-2.8) but not after (SIR=1.3; 95% CI 0.5-2.9) maternal implant surgery; similar excesses were observed among children born before (SIR=2.1; 95% CI 1.5-2.8) and after (SIR=1.6; 95% CI 1.1-2.3) maternal breast reduction surgery. Risks of rheumatic disease were not significantly elevated and were similar among children born before and after maternal breast implant surgery. A borderline significant excess of congenital malformations of the digestive organs was observed among children born after maternal implant surgery (SIR=1.8; 95% CI 1.0-3.1), but a similar excess was observed among children born to women in the breast reduction cohort after their surgeries (SIR=1.9; 95% CI 1.4-2.4). The risk of malformations overall was not significantly higher than expected among children born after cosmetic breast surgery. Any observed elevated risks of adverse health outcomes appear unrelated to breast implants per se, because similar findings were observed among children born both before and after the mother's implant surgery, as well as among children born to control mothers in the breast reduction cohort.

Similarly, a retrospective cohort study conducted in Sweden found no evidence of increased risk of adverse health outcomes among children born to women with breast implants, after a mean follow-up of 8.9 years (range up to 24 years) (Signorello *et al.*, 2001). The investigators evaluated hospitalization rates for rheumatic and esophageal disorders, incidence rates for cancer, and prevalence rates for congenital malformations among 5874 children born to women with cosmetic breast implants compared with 13 274 children born to women who had undergone breast reduction surgery. Compared with children of women who had undergone breast reduction, children of women with cosmetic breast implants were not at increased risk for rheumatic disease (RR=1.1; 95% CI 0.2-5.3), esophageal disorders (RR=1.0; 95% CI 0.7-1.6), congenital malformations overall (RR=1.0; 95% CI 0.6-1.5), congenital malformations specifically involving the digestive organs (RR=0.5; 95% CI 0.2-1.3), cancer (RR=0.3; 95% CI 0.0-2.5) or perinatal death (RR=0.9; 95% CI 0.5-1.8).

A fourth study, conducted in Finland (Hemminki *et al.*, 2004), attempted to evaluate perinatal health outcomes among infants born to women with silicone breast implants, as well as pregnancy and birth patterns among these women. In general, this study suffered from numerous methodological shortcomings, including biased control selection and uncontrolled confounding. As a result of these flaws the null results are uninterpretable.

In summary, there are no demonstrated adverse effects on the offspring of women with breast implants.

6.4.7 Suicide and psychological issues

Five large epidemiologic mortality studies, conducted in various populations during the past decade, have reported with remarkable consistency that women with cosmetic breast implants have a two- to three-fold higher rate of suicide than similar-aged women in the general population (Lipworth *et al.*, 2007; Jacobsen *et al.*, 2004; Brinton *et al.*, 2001,2006; Pukkala *et al.*, 2003; Villeneuve *et al.*, 2006). To our knowledge, prior to these mortality studies, there were no case reports or case series in the literature to suggest a suicide excess among women with cosmetic breast implants. It was an unexpected finding and the only adverse outcome consistently observed in the epidemiologic studies of women with implants. There are no epidemiologic mortality studies or studies of psychological characteristics of women specifically with PIP silicone breast implants.

Three nationwide cohort studies have been conducted in Scandinavia to evaluate cause-specific mortality among women with breast implants. In the Swedish cohort of 3521 women who had breast implants and were followed for an average of 18.7 years (up to 38 years) after implantation, a statistically significant threefold excess rate of suicide compared with the general population was observed base on 24 deaths (SMR=3.0; 95%

CI, 1.9–4.5). The excess rate of suicide in this study became apparent 10 years after implantation and continued to increase with extended follow-up to an SMR of 4.5 (95% CI, 2.6–7.7) among women ten to 19 years after implantation and 6.0 (95% CI, 2.7–13.4) among women 20 or more years after implantation (Lipworth *et al.*, 2007).

Jacobsen *et al.* (2004) reported an increased risk of suicide (SMR = 3.1; 95% CI 1.7-5.2), based on 14 observed suicides compared to an expected 4.5 in the Danish implant cohort of 2788 women with implants, with a mean follow-up of 11.5 years (range, 4-26 years). No clear pattern emerged in the SMRs for suicide according to length of follow-up, with substantial excesses observed in all time periods. This was the first and to date only mortality study to explore pre-implant psychopathology among women undergoing cosmetic breast implant surgery, by examining their pre-operative history of hospitalization for psychiatric illness. The results of this study indicate that the Danish women who underwent breast implantation had a higher prevalence of psychiatric admissions prior to cosmetic surgery (8.0%; 95% CI 7.0%-9.0%) than women who underwent breast reduction (4.7%; 95% CI 4/2%-5.2%) or other types of cosmetic surgery (5.5%; 95% CI 4.5%-6.7%). When compared with all control groups, the risk ratio for prior psychiatric admission was 1.7 (95% CI 1.4-2.0). In fact, seven of 14 women with breast implants who committed suicide in the study had a history of pre-operative psychiatric hospitalization. The study did not, however, provide information on history of specific psychiatric diagnoses or treatments prior to breast implantation.

Brinton *et al.* (2006), in their mortality analysis for the US cohort of 12 144 women who received cosmetic breast implants, reported an increased risk of suicide among implanted women when compared with the general population (SMR = 1.6; 95% CI 1.1-2.3, based on 29 observed suicides) or when compared with other cosmetic surgery patients (RR = 2.6; 95% CI 0.9-7.8). The risk of death from suicide was not elevated during the first ten years of follow-up but was increased in all subsequent time periods.

In the mortality analysis of the large Canadian cohorts (Villeneuve *et al.*, 2006), significantly higher rates of suicide were observed in both the implant (SMR=1.7; 95% CI 1.3-2.2) and other plastic surgery groups (SMR=1.6; 95% CI 1.1-2.2) compared with the general population, based on 58 and 33 observed suicides, respectively. In the Finnish cohort of 2166 women who had cosmetic breast implantation and were followed for a mean of 10.3 years (Pukkala *et al.*, 2003), a statistically significantly increased SMR for suicide was observed among implanted women compared with the general Finnish female population (SMR = 3.2; 95% CI 1.53-5.86, based on 10 suicides compared to an expected 3.1).

In addition to the increased risk of suicide among women with cosmetic breast implants, excesses of other external causes of deaths due to drug and alcohol abuse and dependence, atypical motor vehicle accidents, and other self-harm causes were also reported in the five published mortality studies (Lipworth *et al.*, 2010). The consistently higher rate of suicide, as well as the observed excesses of other drug- and alcohol-related external causes of death, among women with cosmetic breast implants is unlikely to represent a causal association, but rather reflects an increased prevalence of preexisting underlying psychiatric problems and other important risk factors for suicide among a subset of these women prior to their implantation. However, direct empirical research on these women prior to surgery for cosmetic implants is limited.

Women with cosmetic breast implants have been shown to have a higher prevalence of cigarette smoking and alcohol use, younger age at first pregnancy, history of induced abortions, and lower-than-average body weight (Fryzek *et al.*, 2000; Kjoller *et al.*, 2003; Cook *et al.*, 1997; Brinton *et al.*, 2000; Didie and Sarwer 2003), perhaps reflecting an increased prevalence of eating disorders among a subset of these women. Moreover, there is some evidence that women who seek cosmetic breast implantation experience preoperative psychological symptoms indicative of depressive disorders or report a history of psychiatric treatment substantially more frequently than women undergoing other cosmetic surgery (Didie and Sarwer 2003; Sarwer *et al.*, 2000, 2003; Young *et al.*, 1994). These and other characteristics may influence rates of suicide and related causes

of death. The prevalence and severity of pre- and post-implant psychiatric disorders or other factors needs to be further investigated to identify whether some women who undergo cosmetic breast implantation are at high risk of suicide.

There are no studies of PIP silicone breast implants and suicide and related causes of death. However, if women with PIP silicone breast implants are similar in psychological characteristics as women with implants in general, then an excess of suicides and related causes of death would be expected.

6.4.8 Case reports on women with PIP Breast implants

Incident reports collected by the International Confederation for Plastic Reconstructive and Aesthetic Surgery network from Spain, France, UK, Finland, Lebanon, Czech Republic, Italy, Switzerland have raised concerns about unusually high rupture rates in PIP silicone breast implants and lymphadenopathy (with swellings, pain and inflammation), including in lymph nodes far away from the breast, *e.g.*, in the groin, in the neck and in the mediastinum. These lyphadenopathies do not seem to subside after implant removal and can develop even with intact implants. Such a case on lymphadenopathy at a site distant from the implant manifesting itself as cutaneous abnormalities was recently reported for a patient with a PIP implant (Cawrse and Pickford 2011).

No epidemiologic data are available regarding local complications of any kind following implantation with PIP silicone breast implants. If local complication rates of PIP silicone breast implants are similar to other manufacturers' implants, then the issue is likely to be of relatively minor importance in terms of risk to the public health. In a small study on eight explanted PIP silicone breast implants three intracapsular ruptures were identified of which two were symptomatic (Carillon *et al.*, 2012).

No scientific data are available regarding the occurrence of lymphoma of any kind, including ALCL, following implantation with PIP silicone breast implants.

No epidemiologic data on PIP silicone breast implants are available regarding the subsequent occurrence of cancer, including breast cancer. If PIP silicone breast implants are like other implants in regards to subsequent cancer, no association would be expected.

There are no offspring studies of women with PIP silicone breast implants.

There are no studies of PIP silicone breast implants and suicide and related causes of death. However, if women with PIP silicone breast implants are similar in psychological characteristics as women with implants in general, then an excess of suicides and related causes of death would be expected

6.5 Risks related to surgical procedures for breast implantation and explantation

6.5.1 Implant procedure risks

It has been shown in different studies that implant damage at insertion can weaken the implant and probably be responsible, at least in part for a later rupture. Electron microscopy scanning studies of failed implants have shown various types of failure mechanisms, from scalpel, scissor, needle and forceps lesions to abraded, weakened areas, probably caused by surgeons' fingers when they are stuffing an implant into its pocket (Rapaport *et al.*, 1997, Brandon *et al.*, 2001, Wolf *et al.*, 2000).

It should be noted that in many countries a considerable amount of aesthetic breast surgery is done by non-specialized physicians, who frequently do not even have had any

training in basic surgery (*e.g.* Germany). A substantial proportion of the procedures in aesthetic breast surgery are estimated to be done by non-specialists. It is not clear whether this lack of suitable training has a major influence on subsequent breast implant failure rates.

6.5.2 Infection risks

According to the literature, infections are not numerous in the possible complications of breast reconstruction or breast augmentation. They could appear early or be detected as subclinical in the pathogenesis of fibrous contracture.

The early infectious complications after nipple-sparing mastectomy and immediate breast reconstruction with silicone prosthesis are recorded for 5% (2% major infection and 3% minor infection) of the 16% complications in the prospective study of Radovanovic *et al.* (2010). In the study of Siggelkow *et al.* (2004) dedicated to breast implant for cosmetic augmentation or breast reconstruction, the percentage of complication is significantly of higher incidence in patients who had undergone breast reconstruction but still very low («3%).

Some of these early infectious complications could include a Toxic Shock Syndrome linked to toxicogenic *Staphylococcus aureus* and have a dramatic issue if an early diagnosis and prompt initiation of resuscitative and therapeutic measures are not present. But they occur very rarely (Holm & Mühbauer 1998).

Much more frequent is the subclinical infection detected when a reintervention occurs for capsule contracture. They seem to be the source of this contracture in around 30% of the cases and are linked to a biofilm with *Staphylococcus epidermidis* on the breast implant capsule (Pajkos *et al.*, 2003). They need sensitive culture methods for being detected (swabbing is insufficient). For avoiding this phenomenon some surgers are carefully disinfecting the implant before introduction (immersion in a disinfecting solution or antibiotics) and a debate about the role of an eventual interaction between this disinfectant and the membrane of the implant seems to be now closed in the USA (Zambacos *et al.*, 2004).

Meanwhile we may question about an eventual fragility of the shell of PIP silicone breast implants after contact and interaction with a disinfectant if this was not tested before marketing and specified in the notice. This could an eventual cause of more rapid disorders as usual but the data now recorded did not contain any information about this practice and the habits of surgers seem dissimilar.

There were no papers found in the literature dealing with infections linked to contaminated silicone exuding out of the membrane. There are some cases described of granulomas linked to atypical mycobacteria , but all the patients where HIV positive and the source of the bacteria seems to be external and not directly linked to the silicone (Males *et al.*,2010).

No papers were found showing a difference in infections rates between PIP and other protheses. On the other hand one author described recently a zero breast implant infection rate following 1720 PIP silicone implant placements for primary breast augmentation (Keramidas 2009).

No possible microbiological contamination of PIP breast implants was found in the literature. The non-medical silicones are not marketed as " germ free " , thus it could be assumed that the initial contamination of PIP implant may be higher than in the case of implants filled with a certified medical silicone . According to this hypothesis , the applied sterilization process could be insufficient for insuring the level of sterility requested by the European Pharmacopea (one device with a residual contamination for one million of devices after the sterilization process). An increased time of processing, due to an unusual initial contamination could mean more damage to the shell, an insufficient time of sterilization could mean the eventual presence of a microorganism able to grow slowly

in the prosthesis after implantation. The literature survey does not give information about the microflora able to grow in such silicones and the result of sterility control after explantation .

A last issue related to the ethylene oxide sterilization process should be considered. There is a possibility of leakage of residual ethylene oxide from a medical device after ethylene oxide sterilization. In this respect also sterilized PIP silicone breast implants need to be evaluated for conformity with current standards with regard to the level of residual ethylene oxide (EN ISO 10993-7:2008 Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals, EN ISO 10993-7:2008/Cor 1:2009). In case of the presence of excess residual ethylene oxide, inflammation could be induced depending on the level and duration of the contact.

6.5.3 From explanting

Risk of explantation can be subgrouped into risk associated with the anaesthesia and risk of complications from the breast surgery.

Regarding risk from anaesthesia it must be taken into consideration that:

- The overall majority of both cosmetic and reconstructive patients are healthy with no or little comorbidity.
- They have all undergone general anaesthesia to have the implants inserted, so they constitute a selected cohort with respect to that. In subsequent surgeries it is therefore possible with greater precision to judge the individual risk during anaesthesia and surgery.

In modern anaesthesia there is very low risk of death and serious complications, and in daily clinical life both patients and surgeons opt for general anaesthesia in case of complications (for instance capsular contracture) which renders the cosmetic result not satisfactory. This indicates that it is not a matter of great concern neither to patients nor to their physicians.

Regarding risk entailed with the breast surgery, there is always risk of immediate complications: infection and hematoma and delayed complications, the most important being: capsular contracture, malposition, pain, and rupture. The risks of immediate complications are low and rarely a contraindication. The risk of more delayed complications increase in revision surgery as compared with the primary surgery, however, not to an unacceptable level (FDA 2011). The indication for revision surgery should always be balanced with the potential risks of complications and this should be discussed with the patient. For healthy individuals it has been estimated that the risk of death is 1 in 250.000 anaesthesias Lienhart *et al.*, 2006). Anaesthesia may be complicated with aspiration or anaphylaxia. Generally, these risks are in the area of 1 in 6000 – 7000 cases, but lower for healthy persons (Fasting 2010).

Assessment of the risk in different sitations

a) *For explantation in the absence of rupture vs. in the case of rupture*?

Explanting an intact implant is a straight-forward procedure, takes about an hour for bilateral implants and the patient can usually go home the same day or the day after. In cases where the fibrous capsule needs to be removed, the procedure takes a little longer and there is more bleeding both during the procedure and afterwards. The patient is often treated with a drain which can produce secretion for several days. The pain and discomfort for the patient is probably slightly more in case of more extensive dissection, but in-hospital stay not necessarily longer, since patients can be sent home with drain.

b) *For explantation of smooth vs. textured vs. microtextured implants*?

In many cases there is no difference in explanting a smooth versus a textured implant, since many textured implants do not adhere to the surrounding tissue (microtextured

and many textured implants). In cases with high-profile texturing/ large pores in the implant surface there is often in-growth of the capsular tissue into the texturing, but not always. It adheres like glue. In most cases the adherence can be loosened manually or blunt preparation. There are cases where sharp dissection is necessary, which will cause slightly more bleeding and take more time. Exchange of smooth implants can be performed in local anaesthesia if no other procedures are going to take place and if the implant is intact. However, most surgeons and patients prefer general anaesthesia in any case.

c) For explantation in the absence of inflammation vs. in the case of inflammation? (I imagine, no difference regarding the implant. But, what about the removal of lymph nodes?)

If the tissue surrounding the breast implant is marked by inflammation, it is oedematous (containing tissue fluid), swollen and with lots of new tiny blood vessels. The tissue bleeds very easily and can be easy to damage and difficult to repair, sutures may for instance cut through and be difficult to place. If lymph nodes in the axilla are inflamed, painful and swollen it may be best to remove them. This is generally done by a separate incision in the axilla, but more incisions may be needed depending on the localisation of lymph nodes/granulomas to be removed. Any kind of lymph node dissection entails the risk of permanent problems with chronic seroma (accumulation of fluid), nerve damage and in cases of more extensive dissection a risk of lymph oedema – "swollen arm". The need for lymph node removal is not normally included in information to potential breast implantation patients.

d) What are the benefits or avoided risks of explantation?

The benefits of advising for elective (planned) explanting are: controlled circumstances where surgery can be planned within the patient's schedule, easier surgery in case on intact implant, presumably lower risk of complications with the new implant than if a rupture was present. Much lower risk of spilling of free silicone within the tissue, and shorter operation time in case of intact implant. In addition, if the non-medical grade silicone used in some or perhaps PIP silicone breast implants can cause local irritation it would be advisable to remove the implant before problems and symptoms occur rather than after.

e) When rupture has occurred vs. when rupture has not occurred.

In case of rupture of normal breast implants most surgeons advocate removal of the implant. Most patients also seek implant exchange in case of rupture. Several scientific studies indicate that many women have lived for a long period with ruptured implants without knowledge hereof and without occurrence of serious health problems (Hölmich *et al.*, 2001, Brown *et al.*, 2000). However, more local complications, in specific capsular contracture have been found. There is general consensus that implant rupture is rarely an emergency situation. In case of rupture of a PIP implant it seems sound to advice removal of the implant. The non-medical grade silicone gel may cause more tissue reaction than medical grade silicone which often do not cause any reaction. In such cases it would be advised to remove the fibrous capsule surrounding the ruptured implant along with the implant, both to avoid spillage of free silicone into surrounding tissues but also the clear the patient the most from the free non-medical grade silicone.

f) When inflammation has occurred vs. when inflammation has not occurred.

Inflammation is a reversible reaction, but can progress to fibrosis if the irritant persists/cannot be removed completely. Avoidance of inflammation is indeed preferable. Inflammation can be found by microscopy and may not always be clinically relevant, if the changes are minor. In case of clinical symptoms of inflammation (pain and swollen tissue), the microscopic changes are generally marked. If the patient has symptoms of inflammation there is a need to remove the implant as well as the surrounding fibrous capsule. Lymph nodes with marked inflammation and pain should also be removed and the patient should be followed regularly to identify potential progression and need for

additional surgery. If the inflammation includes breast tissue, muscle on the chest or skin it may be necessary to excise these structures, which can impair both function as well as the cosmetic result heavily. In case of silicone spread to the axilla along facial planes as can be seen for instance after an accident it can be necessary to remove silicone from the nerves in the brachial plexus. This situation is fortunately very rare. In case of local irritation from such silicone the long-term complications due to advancing fibrosis can be devastating.

g) *When lymph nodes have significantly swollen vs. have incurred the benign swelling generally associate with all silicon breast implants.*

Many women with silicone breast implants have lymph nodes in the axilla containing silicone. This is often due to migration of short chained silicone oils. In case of implant rupture also longer chained particles can be taken up in the regional lymph nodes. Normally such lymph nodes are not painful, only enlarged. But in case of inflammation, this is often accompanied by pain. There is no scientific evidence that containment of medial grade silicone within asymptomatic lymph nodes possesses any health threat. Enlarged lymph nodes may cause both patients and clinicians concern, however, the diagnosis is easily made by ultrasonography and in equivocal cases a fine needle aspiration. Lymph nodes in implant patients are normally only removed if they cause significant pain and distress, and this is rare.

7 Overall conclusions on the risks and benefits from PIP and other breast implants

7.1 General considerations

Regardless of manufacturer, a number of silicone breast implants will fail at some point after implantation. The risk factors for failure may be identified, namely:

a) The implant procedure. It has been shown in different studies that implant damage at insertion can weaken the implant and probably be responsible, at least in part for a later rupture. Electron microscopy scanning studies of failed implants have shown various types of failure mechanisms, from scalpel, scissor, needle and forceps lesions to abraded, weakened areas, probably caused by surgeons' fingers when they are stuffing an implant into its pocket. There is an estimation that a substantial proportion of the procedures in aesthetic breast surgery are carried out by non-specialists It is not clear whether this lack of suitable training is a major influence on subsequent breast implant failure rates

b) Time since the implantation. Breast implants can fail, regardless of manufacturer, and the probability of failure increases with time since implantation. This phenomenon is true for all types of implants used in the human body. Differences in diagnostic criteria and implant time in situ might account for large discrepancies in the reported number of ruptures in different clinical studies.

c) Physical and chemical features of the implant. Most implants comprise a single envelope. Besides breast implants a variety of medical devices are manufactured composed of silicone elastomers. The quality and purity of the silicone elastomer along with the effectiveness of the control over the chemical reaction for generating the gel can have a marked influence over the physical and chemical properties of a breast implant. The implants may on occasion have small, difficult to detect pinhole defects. Defects such as tiny cracks are sometimes also found where the posterior patch is 'welded' to the remaining implant.

d) Patient specific factors. There are two considerations, patient factors that may influence the integrity of the implant and factors that may influence the effects of leaked components. Apart from possible impacts of accidents rather little has been published on the influence of life style factors on breast implant integrity. The primary factors

influencing patient vulnerability to leaked implant contents are also rather poorly researched.

7.2 Assessment of PIP silicone breast implants

There is no evidence that women who have had PIP silicone breast implants differ significantly initially in health status from those having implants from other manufacturers.

Important difficulties in making an assessment of the risks from PIP silicone breast implants are:
*in some countries and in some women it is quite uncertain whether PIP silicone breast implants were used until explantation has been carried out.

*Reporting of breast implant failure and of any adverse effects on health due to this is not obligatory and consequently reported incident rates are frequently unreliable.

The SCENHIR is aware that PIP silicone breast implants have been found to vary considerably in composition and as a result are likely to vary substantially in performance characteristics. No clear temporal trend of implant problems has been identified for PIP silicone breast implants. Consequently it is very difficult to identify a truly representative PIP implant for risk assessment purposes.

The data available on PIP silicone breast implants is inevitably limited at this stage. The focus of attention in this initial response is on the following aspects:

- Physical and chemical properties of the PIP silicone breast implants, where available
- Findings of the effects of PIP implant contents in the required animal tests, where available
- Reports of incidents of PIP implant failures, where available

Physical and chemical properties. The more recent PIP silicone breast implants, in common with those of other manufacturers, comprise a single envelope/shell. The implants consist of an outer shell filled with a gel. In common with those of most other manufacturers, they were manufactured using the polymer polydimethylsiloxane, also known as silicone. The chemical reaction resulting in crossed linked gel formation must be controlled because it governs the degree of crosslinking. The more variable the reaction, the greater the variation of the content of volatile and/or low molecular mass components in the implant (gel and shell). Use of industrial grade silicone along with a lesser control of the cross linking process appears to be associated with a higher content of low molecular weight components. As a consequence of the migration of these components it is reasonable to conclude that the shell might be weakened and that components could leak into the surrounding tissue. Tests conducted by the French Authorities on the physical integrity of a sample of PIP silicone breast implants indicated weaknesses in PIP shells not found in other commercially available implant.

Findings in Toxicity tests**.** ,A range of assays can be selected. For implant devices with prolonged contact the most extensive toxicity testing is indicated including cytotoxicity, sensitization, irritation, acute and subchronic systemic toxicity, genotoxicity, and implantation tests. Additional tests may be indicated by the risk assessment that is performed of a certain medical device/constituent such as biodegradation and toxicokinetic studies, chronic toxicity, carcinogenicity, immunotoxicity, neurotoxicity and reproductive/developmental toxicity. To date few studies aimed at evaluating the toxicity of the contents of PIP silicone breast implants have been conducted using tests specified for assessing the safety of grade III medical devices . The tests that were performed are designed to assess cytotoxicity, irritancy and genotoxicity. Medical grade silicone gels give negative results in these tests. In the case of the contents of the PIP silicone breast implants, tests for cytotoxicity and genotoxicity were negative. However, an *in vivo* test for irritancy was positive. This indicates the potential for inducing local irritancy when the silicone gel is released form the implant. The extent will depend on the amount released and local conditions. The implications of this positive result for irritancy,

for women with PIP silicone breast implants, is currently uncertain and requires further investigation.

Incident reports. There are various methods to identify implant failure**.** It is important to note that clinical breast examinations alone have little sensitivity for detecting implant rupture. If there are also clinical signs of adverse effects then a follow up is likely to take place but a clinical examination is likely to miss implant rupture in the absence of positive signs. There is international agreement among professional radiologists and reconstructive and aesthetic surgeons that Magnetic Resonance Imaging (MRI) is by far the most accurate modality. Ultrasonography is the second best imaging modality for detecting implant rupture, but it is less precise and more operator dependent . Mammography is less useful.

There are cases reported suggesting that PIP silicone breast implants may have a higher failure rate in the first few years after implantation compared with those from other breast implant manufacturers. There are also a few case reports that ruptured PIP silicone breast implants may be associated with a higher incidence of swollen and painful lymph nodes.

The limited and selective clinical data and the absence of epidemiologic data on PIP silicone breast implants provide insufficient evidence to warrant a conclusion that women with PIP silicone breast implants have a greater risk to their health than women with breast implants from other manufacturers. However, when the limited available information is taken together with the findings from tests of the physical and chemical properties of the shell and silicone and of the *in vivo* irritancy test, the possibility of health effects cannot be ruled out.

7.3 Generic Risks and Benefits of removal of PIP silicone breast implants

From a public health perspective it is important to identify generic risks and benefits. Such an assessment may not necessarily apply to an individual patient however.

As noted above there are obvious difficulties in providing scientifically based generic advice because:

* Over time, regardless of the manufacturer there will be an increased failure rate of the implants

*For many women it is uncertain whether their breast implant is a PIP manufactured implant

*Simple clinical examination alone is unlikely to identify those patients with a leaking/ruptured implant.

*Many such implants have been inserted by surgeons who are not qualified in plastic surgery . This might be a source of higher failure rates among their patients.

It is important to identify as far as possible high risk categories of patients based on the identified risk factors noted above. Manufacturer, duration of implant,, patient symptoms and psychological state have been identified. However these criteria are insufficiently established at present and a patient by patient approach is therefore required. It is important that the risks identified in this opinion are considered in the light of the risks involved in prophylactic explantation.

7.4 Recommendations for further work

The SCENIHR recommends that further work is undertaken as a priority to establish with greater certainty the type and magnitude of health risks, if they exist, associated with PIP silicone breast implants.

In particular:

* A thorough assessment of the composition of a range of PIP explants

* Further assessment of biological effects of the silicone gel used in PIP silicone breast implants/explants

*The need for simple tests that can be used for routine reliable low cost screening

* The establishment of reliable data reporting procedures for silicone breast implants and nationwide data bases on SBI failures and other implant failures and the health effects of such failures. This should be a joint undertaking involving national governments, implant manufacturers and plastic surgeons.

* Research on explants to identify cause of failure The FDA guidance document for saline, silicone gel, and alternative breast implants (FDA Nov. 2006) recommends the protocol developed by Brandon, *et al.* (2003a) for testing and analyzing explants. The FDA emphasizes detailed mechanical testing, scanning electron microscopy analysis (SEM), detailed chemical analysis, and comparison with a control group of unimplanted devices. It is recommended that this protocol be established as the "International Protocol for Testing and Analyzing Explants and Controls". A standardized protocol would allow different laboratories throughout the world to compare their data.

A retrieval and analysis study of PIP explants and controls should be established using this protocol. The mechanical tests should include tensile strength, elongation, force-to-break, moduli, and tear resistance. The SEM examination should include an analysis of shell failure sites to determine the cause of failure and an overall characterization of explant and shell surfaces, emphasizing regions of shell degradation. Chemical analysis would involve extracting the non-crosslinked, low molecular weight silicones from the shell in order to determine the percent swelling. The extract should be analyzed to identify the low molecular weight silicone constituents in the shell. In addition platinum levels should be measured in the shell and the gel. Considering the various types of PIP silicone breast implants that have been manufactured, explants should be tested to determine if one particular type of PIP implant is failing or if failure is attributed to all types.

There are several types of diagnostic techniques available to analyze ruptured implants for failure mechanisms. Visual inspection, physical examination, and photographic analysis provide an overall description of the implant shape and gross features of the shell failure region. These techniques allow categorization and documentation of the mode of failure and are quite useful as a supplemental tool in the diagnosis of implant failure mechanisms. Microscopy techniques provide details of the ruptured shell region and can be used to determine the cause of breast implant failure. The use of field emission scanning electron microscopy (SEM) provides the state-of-the-art technique in the analysis of ruptured breast implants. Retrieval and analysis studies have used scanning electron microscopy to describe the morphology of several types of breast implant failures.

* Improved testing protocols The testing procedures and standards for breast implants should be refined to consider the interaction of the shell material with the filling gel and the surrounding body fluids, with respect to fatigue and tear resistance behaviour of the shell and the total implant.

8 OPINION

Mandate

To determine whether implanted PIP breast implants could give reasons for concern from the health point of view when compared with state of the art implants, taking into account their structure, composition and detected defects (*e.g.* low quality silicon, single envelop instead of double envelop) and the risk of rupture and oozing they may present;

General response

The data available presently on PIP silicone breast implants is necessarily limited at this stage, as the PIP manufacturer did no clinincal or epidemiologic research. So, the

evidence on failure rates and complications related to PIP silicone breast implants are based on case reports. The large number of breast implant studies conducted to date and reported in the literature did not for the most part examine data by manufacturer. The focus of attention in this initial response is on the following aspects:

- Physical and chemical properties of the PIP silicone breast implants, where available
- Findings of the effects of PIP implant contents in the required animal tests, where available
- Reports of incidents of PIP implant failures, where available

Physical and chemical properties. The more recent PIP silicone breast implants, in common with those of other manufacturers, comprise a single envelope/shell. The implants consist of an outer shell filled with a gel. In common with those of most other manufacturers, they were manufactured using the polymer polydimethylsiloxane, also known as silicone. The chemical reaction resulting in gel formation must be controlled because it governs the degree of crosslinking. The more variable this reaction is, the greater the variation of the content of volatile and/or low molecular mass components in the implant (gel and shell) is likely to be. Use of industrial grade silicone along with a lesser control of the cross linking process appears to be associated with a higher content of low molecular weight components. As a consequence of the migration of these components it is reasonable to conclude that the shell might be weakened and that components could leak into the surrounding tissue. Tests conducted by the French Authorities on the physical integrity of a sample of PIP silicone breast implants indicated weaknesses in PIP shells not found in other commercially available implant.

Findings in Toxicity tests. To date few studies aimed at evaluating the toxicity of the contents of PIP silicone implants sofar have been conducted using tests specified for assessing the safety of grade III medical devices. The tests that were performed are designed to assess cytotoxicity, irritancy and genotoxicity. Medical grade silicone gels give negative results in these tests. In the case of the contents of the PIP silicone implants, tests for cytotoxicity and genotoxicity were negative. However, an *in vivo* test for irritancy was positive. This indicates the potential for inducing local irritancy when the silicone gel is released form the implant. The extent will depend on the amount released, the duration of exposure and other local conditions. The implications of this positive result for irritancy for women with PIP silicone implants are currently uncertain and require further investigation.

Incident reports. There are cases reported suggesting that PIP silicone breast implants may have a higher failure rate in the first few years after implantation compared with those from other breast implant manufacturers. There are also a few case reports that ruptured PIP silicone implants may be associated with a higher incidence of swollen and painful lymph nodes.

The limited and selective clinical data and the absence of epidemiologic data on PIP silicone breast implants provide insufficient evidence to warrant a conclusion that women with PIP silicone breast implants have a greater risk to their health than women with breast implants from other manufacturers. However, studies among women with standard-quality implants (including patient with ruptured implants) have shown that the risks of cancer and connective tissue disease are not increased among women with such implants. The limited available information, allied with the findings from tests of the physical and chemical properties of the shell and silicone and of the *in vivo* irritancy test, raises some concerns about the safety of PIP silicone breast implants as the possibility of health effects cannot be ruled out.

The SCENIHR is asked to identify the generic risks and benefits of various actions that might be taken to address these concerns. As noted above there are obvious difficulties in providing scientifically based advice because:

- Over time, regardless of the manufacturer there will be an increased failure rate of the implants;

- For many women it is uncertain whether their breast implant is a PIP manufactured implant;
- Simple clinical examination alone is unlikely to identify those patients with a leaking/ruptured implant;
- Many such implants have been inserted by surgeons who are not qualified in plastic surgery. This might be a source of higher failure rates among their patients.

It is important to identify as far as possible high risk categories of patients based on the identified risk factors noted above. Manufacturer, duration of implant,, patient symptoms and psychological state have been identified. However these criteria are insufficiently established at present and a patient by patient approach is therefore required. It is important that the risks identified in this opinion are considered in the light of the risks involved in unnecessary explantation.

Question 1A: What is the global reported incident rate associated with PIP breast implants;

Currently available data do not allow a reliable estimate

Question 1B: How does this compare with the global reported incident rate for other breast implants;

Currently available data do not allow a reliable estimate

Question 1C: What percentage of this global reported incident rate is associated with rupture of PIP breast implants?

Currently available data do not allow a reliable estimate

Question 1D: What percentage of this global reported incident rate for PIP implants is associated with other adverse effects on health and what are these adverse health effects?

Currently available data do not allow a reliable estimate

Question 1E: Is there evidence that PIP breast implants are more difficult to explant, before or after rupture, in comparison with other breast implants;

The evidence although limited indicates that there is no difference provided the device and fibrous capsule is intact. If the device has ruptured and particularly if it has caused substantial inflammation then the removal is more difficult. Thus a higher rupture rate of an implant made by a particular manufacturer would be problematic.

Question 1F: Is there evidence of any increased report of lymph node complications associated with the PIP breast implants?

There is evidence from an animal study of increase in irritancy. In contrast medical grade silicone gel does not cause detectable irritation in animal models. There is limited case history data in PIP explant patients indicating a possible increase in lymph node swelling and painful lymph nodes. It should be noted, however, that there may be overreporting of such conditions. This may arise due to reporting and ascertainment biases as a consequence of the widespread concern generated by media reporting on PIP silicone breast implants when compared to reporting of these conditions in non-PIP implant patients.

Question2

In case reasons for concern related to implanted PIP breast implants are identified, to make a risk/benefit analysis of explantation.

The evidence to date, indicating a health risk for women with PIP silicone breast implants, is not strong. However there is some concern regarding an increased inflammation from ruptured PIP silicone breast implants. It is not possible to make a general risk benefit statement at this time. Rather, for the time being, the risk benefit

assessment needs to be based on a patient by patient basis by the aesthetic surgeon, bearing in mind the time since the implantation and the psychological state of the patient.

7 MINORITY OPINION

None.

8 REFERENCES

Adams WP, Jr., Robinson JB, Jr., Rohrich RJ. (1998) Lipid infiltration as a possible biologic cause of silicone gel breast implant aging. Plast Reconstr Surg 101(1):64-68.

Ahn CY, DeBruhl ND, Gorczyca DP, Shaw WW, Bassett LW. (1994) Comparative silicone breast implant evaluation using mammography, sonography, and magnetic resonance imaging: experience with 59 implants. Plast Reconstr Surg 94(5):620-627.

Ahn CY, Shaw WW. (1994) Regional silicone-gel migration in patients with ruptured implants. Ann Plast Surg 33(2):201-208.

ASTM E305 - 07 Standard Practice for Establishing and Controlling Atomic Emission Spectrochemical Analytical Curves. American Society for Testing and Materials (ASTM), West Conshohocken, PA, USA.

Bartel D R (1994), Re: Sclerodermalike esophageal disease in children of mothers with silicone breast implants (letter), JAMA, 272, 767.

Beekman WH, Feitz R, Hage JJ, Mulder JW. (1997) Life span of silicone gel-filled mammary prostheses. Plast Reconstr Surg 100(7):1723-1726.

Beekman WH, Feitz R, van Diest PJ, Hage JJ. (1997) Migration of silicone through the fibrous capsules of mammary prostheses. Ann Plast Surg 38(5):441-445.

Bengtson BP, Van Natta BW, Murphy DK, Slicton A, Maxwell GP, Style 410 US Core Clinical Study Group. (2007) Style 410 highly cohesive silicone breast impant core study results at 3 years. Plast Reconstruct Surg 120(7 Suppl 1):40S-48S

Berg WA, Caskey CI, Hamper UM, Kuhlman JE, Anderson ND, Chang BW *et al.* (1995) Single- and Double-Lumen Silicone Breast Implant Integrity: Prospective Evaluation of MR and US Criteria. Radiology 197(1):45-52.

Birkefeld AB, Eckert H, Pfleiderer B. (2004) A study of the aging of silicone breast implants using 29Si, 1H relaxation and DSC measurements. Biomaterials 25(18):4405-4413.

Blackburn W D Jr and Everson M P (1997), Silicone-associated rheumatic disease: an unsupported myth, Plast Reconstr Surg, 99, 1362-1367.

Bokobza L (2004) Elastomeric Composites. I Silicone Composites. Journal of Applied Polymer Science, Vol. 93, 2095-2104,

Bondurant S, Ernster V and Herdman R (1999), Safety of Silicone Breast Implants, Report of the Committee on the Safety of Silicone Breast Implants (IOM), Washington, D.C., National Academy Press

Brandon HJ, Jerina KL, Wolf CJ, Young VL. (2002) *In vivo* aging characteristics of silicone gel breast implants compared to lot-matched controls. Plast Reconstr Surg 109(6):1927-1933.

Brandon HJ, Jerina KL, Wolf CJ, Young VL. (2003) Biodurability of retrieved silicone gel breast implants. Plast Reconstr Surg 111(7):2295-2306.

Brandon HJ, Taylor ML, Powell TE, Walker PS. (2006) Morphology of breast implant fold flaw failure. J Long Term Eff Med Implants 16(6):441-450.

Brandon HJ, Young VL, Jerina KL, Wolf CJ. (2001) Scanning electron microscopy characterization of surgical instrument damage to breast implants. Plast Reconstr Surg 108(1):52-61.

Brandon HJ, Young VL, Jerina KL, Wolf CJ. (2001b) Variability in the properties of silicone gel breast implants. Plast Reconstr Surg 108(3):647-655.

Brandon HJ, Young VL, Watson ME, Wolf CJ, Jerina KL. (2003a) Protocol for retrieval and analysis of breast implants. J Long-Term Effects Med Implants 13(1) 49-61

Breiting V B, Holmich L R, Brandt B, Fryzek J P, Wolthers M S, Kjoller K, McLaughlin J K, Wiik A and Friis S (2004), Long-term health status of Danish women with silicone breast implants, Plast Reconstr Surg, 114, 217-226

Brinton L A, Brown S L, Colton T, Burich M C and Lubin J (2000b), Characteristics of a population of women with breast implants compared with women seeking other types of plastic surgery, Plast Reconstr Surg, 105, 919-927

Brinton L A, Buckley L M, Dvorkina O, Lubin J H, Colton T, Murray M C and Hoover R (2004), Risk of connective tissue disorders among breast implant patients. Am J Epidemiol, 160, 619-627.

Brinton L A, Lubin J H, Burich M C, Colton T and Hoover R N (2001b), Mortality among augmentation mammoplasty patients, Epidemiology, 12, 321-326

Brinton L A, Lubin J H, Burich M C, Colton T, Brown S L and Hoover R N (2000a), Breast cancer following augmentation mammoplasty, Cancer Causes Control, 11, 819-827

Brinton L A, Lubin J H, Burich M C, Colton T, Brown S L and Hoover R N (2001a), Cancer risk at sites other than the breast following augmentation mammoplasty, Ann Epidemiol, 11, 248-256

Brinton L A, Lubin J H, Murray M C, Colton T and Hoover R N (2006), Mortality rates among augmentation mammoplasty patients: an update, Epidemiology, 17, 162-169

Brinton L A, Malone K E, Coates R J, Schoenberg J B, Swanson C B, Daling J R and Stanford J L (1996), Breast enlargement and reduction: results from a breast cancer case-control study, Plast Reconstr Surg, 97, 269-275

Brisson J, Holowaty EJ, Villeneuve P J, Xie L, Ugnat A M, Latulippe L and Mao Y (2006), Cancer incidence in a cohort of Ontario and Quebec women having bilateral breast augmentation, Int J Cancer, 118, 2854-2862

Brody GS (2009), http:, www.emedicine.com/plastic/topic500.htm. Breast Implants, Silicone: Safety and Efficacy. Ref Type: Internet Communication

Brody G, Deapen D, Gill P (2010), T-cell non Hodgkin's anaplastic lymphoma associated with one style of breast implants, In: 89th Annual Meeting, American Association of Plastic Surgeons, San Antonio, TX.

Brook MA (2006) Platinum in silicone breast implants. Biomaterials 27, 3274-3286

Brown SL, Middleton MS, Berg WA, Soo MS, Pennello G. (2000) Prevalence of rupture of silicone gel breast implants revealed on MR imaging in a population of women in Birmingham, Alabama. AJR Am J Roentgenol 175(4):1057-1064.

Brown S L, Pennello G, Berg W A, Soo M S and Middleton M S (2001), Silicone gel breast implant rupture, extracapsular silicone, and health status in a population of women, J Rheumatol, 28, 996-1003.

Brown SL, Silverman BG, Berg WA. (1997) Rupture of silicone-gel breast implants: causes, sequelae, and diagnosis. Lancet 350(9090):1531-1537.

Bryant H and Brasher P (1995), Breast implants and breast cancer - reanalysis of a linkage study, N Engl J Med, 332, 1535-1539

Burns C J, Laing T J, Gillespie B W, Heeringa S G, Alcser K H, Mayes M D, Wasko M C M, Cooper B C, Garabrant D H and Schottenfeld D (1996), The epidemiology of scleroderma among women: Assessment of risk from exposure to silicone and silica, J Rheumatol, 23, 1904-1911.

Caffee HH. (1986) The influence of silicone bleed on capsule contracture. Ann Plast Surg 17(4):284-287.

Carillon MA, Giard S, Emmanuelli V, Houpeau JL, Ceugnart L, Chauvet MP (2012) Breast implants and health alert PIP: experience of the regional cancer center of Lille. Bull Cancer. 2012 Jan 19. [Epub ahead of print]

Cawrse NH, Pickford MA. (2011) Cutaneous manifestation of silicone dissemination from a PIP implant. A case for prophylactic explantation? J Plast Reconstr Aesthet Surg 64 (8) e208-209.

Cher DJ, Conwell JA, Mandel JS. (2001) MRI for detecting silicone breast implant rupture: meta-analysis and implications. Ann Plast Surg 47(4):367-380.

Chung KC, Greenfield ML, Walters M. (1998) Decision-Analysis Methodology in the Work-up of Women with Suspected Silicone Breast Implant Rupture. Plast Reconstr Surg 102(3):689-695.

Cohen BE, Biggs TM, Cronin ED, Collins DR, Jr. (1997) Assessment and longevity of the silicone gel breast implant. Plast Reconstr Surg 99(6):1597-1601.

Collins N, Sharpe DT.(2000) Silicone Gel-Filled Breast Implant Integrity: A Retrospective Review of 478 Consecutivly Explanted Implants. Plast Reconstr Surg 105(6):1979-1985.

Collis N, Litherland J, Enion D, Sharpe DT. (2007) Magnetic resonance imaging and explantation investigation of long-term silicone gel implant integrity. Plast Reconstr Surg 120(5):1401-1406.

Cook R R (1994), Re: Sclerodermalike esophageal disease in children of mothers with silicone breast implants (letter), JAMA, 272, 767-768.

Cook RR, Bowlin SJ, Curtis JM, Hoshaw SJ, Klein PJ, Perkins LL *et al.* (2002) Silicone gel breast implant rupture rates: research issues. Ann Plast Surg JID - 7805336 48(1):92-101.

Cook L S, Daling J R, Voigt L F, deHart M P, Malone K E, Stanford J L, Weiss N S, Brinton L A, Gammon M D and Brogan D (1997), Characteristics of women with and without breast augmentation. JAMA, 277, 1612-1617

Cook RR, Hoshaw SJ, Perkins LL.(1999) Failure of silicone gel breast implants. Plast Reconstr Surg 103(3):1091-1092.

Council Directive 90/385/EEC on the approximation of laws of the Member States relating to active implantable medical devices (hereafter AIMDD), (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1990L0385:20071011:en:PDF)

Council Directive 93/42/EEC concerning medical devices (hereafter MDD), (http://eurex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1993L0042:20071011:EN:PDF).

Cunningham B (2007), The Mentor core study on silicone MemoryGel breast implants, Plast Reconstr Surg, 120, 19S-29S.

Cunningham B, McCue J. (2009) Safety and effectiveness of Mentor's MemoryGel implants at 6 years. Aesthetic Plast Surg 33(3):440-444.

De Angelis GA, de Lange EE, Miller LR, Morgan RF. (1994) MR imaging of breast implants. Radiographics 14(4):783-794.

Deapen D M, Bernstein L and Brody G S (1997), Are breast implants anticarcinogenic? A 14-year follow-up of the Los Angeles study, Plast Reconstr Surg, 99, 1346-1353

Deapen D, Hamilton A, Bernstein L and Brody G S (2000), Breast cancer stage at diagnosis and survival among patients with prior breast implants, Plast Reconstr Surg, 105, 535-540

Deapen DM, Hirsch EM, Brody GS. (2007) Cancer risk among Los Angeles women with cosmetic breast implants. Plast Reconstr Surg 119(7):1987-1992.

De Camara DL, Sheridan JM, Kammer BA. (1993) Rupture and aging of silicone gel breast implants. Plast Reconstr Surg (5):828-834.

De Jong D, Vasmel W L E, de Boer J P, Verhave G, Barbe E, Casparie M K and van Leeuwen F E (2008), Anaplastic large-cell lymphoma in women with breast implants, JAMA 300, 2030-2035.

Didie E R and Sarwer D B (2003), Factors that influence the decision to undergo cosmetic breast augmentation surgery, J Womens Health, 12, 241-253

Directive 98/79/EC of the European Parliament and of the Council on in vitro diagnostic medical devices (hereafter IVDD). (http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=CONSLEG:1998L0079:20090807:EN:PDF)

DIRECTIVE 2003/12/EC of 3 February 2003 on the reclassification of breast implants in the framework of Directive 93/42/EEC concerning medical devices

http://eur-lex.europa.eu/LexUriServ/LexUriServ.do?uri=OJ:L:2003:028:0043:0044:en:PDF

Dowden RV. (1993) Definition of terms for describing loss of gel from breast implants. AJR Am J Roentgenol 160(6):1360.

Dowden RV. (1993) Detection of gel implant rupture: a clinical test. Plast Reconstr Surg 91(3):548-550.

Dowden R. (1999) Re: The life span of silicone gel breast implants and a comparison of mammography, ultrasonography, and magnetic resonance imaging in detecting implant rupture: a meta-analysis [letter; comment]. Ann Plast Surg 43(1):99-100.

Dugowson C E, Daling J, Koepsell T D, Voigt L and Nelson J L (1992), Silicone breast implants and risk for rheumatoid arthritis. 56th Annual Meeting. American College Rheumatology, Arthr Rheum, 35(Suppl), S66.

Duvic M, Moore D, Menter A and Vonderheid E C (1995), Cutaneous T-cell lymphoma in association with silicone breast implants, J Am Acad Dermatol, 32, 939-942.

Edworthy S M, Martin L, Barr S G, Birdsell D C, Brant R F and Fritzler MJ (1998), A clinical study of the relationship between silicone breast implants and connective tissue disease, J Rheumatol, 25, 254-260.

Eisenberg HV, Bartels RJ. (1977) Rupture of a silicone bag-gel breast implant by closed compression capsulotomy: case report. Plast Reconstr Surg 59(6):849-850.

Eklund G W, Busby R C, Miller S H, Job J S (1988), Improved imaging of the augmented breast, AJR Am J Roentgenol, 151, 469-473.

Englert H, Joyner E, McGill N, Chambers P, Horner D, Hunt C *et al.* (2001) Women's health after plastic surgery. Intern Med J 31(2):77-89.

Englert H, Morris D and March L (1996), Scleroderma and silicone gel breast prostheses--the Sydney study revisited, Aust N Z J Med, 26, 349-355.

EN ISO 10993-1:2009. Biological evaluation of medical devices -- Part 1: Evaluation and testing within a risk management process. ISO, Geneva, Switzerland, CEN, Brussels, Belgium 2009.

EN ISO 10993-7:2008 Biological evaluation of medical devices – Part 7: Ethylene oxide sterilization residuals, EN ISO 10993-7:2008/Cor 1:2009 ISO, Geneva, Switzerland, CEN, Brussels, Belgium 2009.

EN ISO 14155:2011. Clinical investigation fo medical devices for human subjects – good clinical practice. ISO, Geneva, Switzerland, CEN, Brussels, Belgium 2011.

EN ISO 14607;2007 Non active surgical implants – mammary implants – particular requirements. ISO, Geneva, Switzerland, CEN, Brussels, Belgium, 2007

EN ISO 14630:2008 Non active surgical implants – general requirements. ISO, Geneva, Switzerland, CEN, Brussels, Belgium, 2008

EN ISO 14971:2009. Medical devices -- Application of risk management to medical devices. ISO, Geneva, Switzerland, 2007, CEN, Brussels, Belgium 2009.

Epstein, W A (1994), Re: Sclerodermalike esophageal disease in children of mothers with silicone breast implants (letter), JAMA, 272, 768.

European Committee on Quality Assurance and Medical Devices in Plastic Surgery (EQUAM) (2000), Consensus declaration on breast implants, 23-6-2000: 4th Consensus Declaration, Israel, European Committee on Quality Assurance

Everson LI, Parantainen H, Detlie T, Stillman AE, Olson PN, Landis G *et al.* (1994) Diagnosis of breast implant rupture: imaging findings and relative efficacies of imaging techniques. AJR Am J Roentgenol 163(1):57-60.

Fajardo L L, Harvey J A, McAleese K A, Roberts C C and Granstrom P (1995), Breast cancer diagnosis in women with subglandular silicone gel-filled augmentation implants, Radiology, 194, 859-862.

Fasting S (2010) Risk in anaesthesia. Tidsskr Nor laegeforen 130(5); 498-502 (In Norwegian)

FDA (2006) Guidance for industry and FDA staff – Saline, Silicone Gel, and Alternative breast implants. FDA, Washington, USA. http://www.fda.gov/cdrh/breastimplants/siliconegel.html

FDA (2011) FDA update on the safety of silicone gel-filled breast implants. June 2011.\\\\ http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/UCM260139.pdf

FDA (2011) Anaplastic large cell lymphoma (ALCL) in women with breast implants: preliminary FDA findings and analysis. FDA, Washington, DC, USA. http://www.fda.gov/downloads/MedicalDevices/ProductsandMedicalProcedures/ImplantsandProsthetics/BreastImplants/UCM240003.pdf

Feng LJ, Amini SB. (1999) Analysis of risk factors associated with rupture of silicone gel breast implants. Plast Reconstr Surg 104(4):955-963.

Friis S, Hölmich LR, McLaughlin J K, Mellemkjaer L, Kjoller K, Fryzek J P, Henriksen T and Olsen J H (2006), Cancer risk among Danish women with cosmetic breast implants, Int J Cancer, 118, 998-1003

Friis S, Mellemkjaer L, McLaughlin J K, Breiting V, Kjaer S K, Blot W and Olsen J H (1997), Connective tissue disease and other rheumatic conditions following breast implants in Denmark, Ann Plast Surg, 39, 1-8.

Fryzek JP, Hölmich L, McLaughlin JK, Lipworth L, Tarone RE, Henriksen T *et al.* (2007) A Nationwide Study of Connective Tissue Disease and Other Rheumatic Conditions Among Danish Women With Long-Term Cosmetic Breast Implantation. Ann Epidemiol 17(5):374-379.

Fryzek JP, Signorello LB, Hakelius L, Feltelius N, Ringberg A, Blot WJ *et al.* (2001a) Self-reported symptoms among women after cosmetic breast implant and breast reduction surgery. Plast Reconstr Surg 107(1):206-213.

Fryzek J P, Weiderpass E, Signorello L B, Hakelius L, Lipworth L, Blot W J, McLaughlin J K and Nyren O (2000), Characteristics of women with cosmetic breast augmentation surgery compared with breast reduction surgery patients and women in the general population of Sweden, Ann Plast Surg, 45, 349-356

Gabriel S E, O'Fallon W M, Kurland L T, Beard C M, Woods J E and Melton LJ III (1994), Risk of connective-tissue diseases and other disorders after breast implantation, N Engl J Med, 330, 1697-1702

Gedalia A, Cuellar M L and Espinoza L R (1995), Skin rash and anti-Ro/SS-A antibodies in an infant from a mother with silicone breast implants, Clin Exp Rheumatol, 13, 521-523.

Gaudet G, Friedberg J W, Weng A, Pinkus G S and Freedman A S (2002), Breast lymphoma associated with breast implants: two case reports and a review of the literature, Leuk Lymphoma, 43, 115-119.

Giltay E J, Bernelot Moens H J, Riley A H and Tan R G (1994), Silicone breast prostheses and rheumatic symptoms: A retrospective follow up study, Ann Rheum Dis, 53, 194-196.

Goldberg EP, Widenhouse C, Marotta J, Martin P. (1997) Failure of silicone gel breast implants: analysis of literature data for 1652 explanted prostheses [letter,]. Plast Reconstr Surg 100(1):281-284.

Goldman J A, Greenblatt J, Joines R, White L, Aylward B and Lamm S H (1995), Breast implants, rheumatoid arthritis, and connective tissue diseases in clinical practice, J Clin Epidemiol, 48, 571-582.

Goodman CM, Cohen V, Thornby J, Netscher D. (1998) The life span of silicone gel breast implants and a comparison of mammography, ultrasonography, and magnetic resonance imaging in detecting implant rupture: a meta-analysis. Ann Plast Surg 41 (6) 577-585

Gorczyca DP, Debruhl ND, Ahn CY, Hoyt A, Sayre JW, Nudell P *et al.* (1998) Silicone breast Implant ruptures in an Animal Model: comparison of Mammography, MR Imaging, US and CT. Radiology 190(1):227-232.

Greenwald DP, Randolph M, May-JW J. (1996) Mechanical analysis of explanted silicone breast implants. Plast Reconstr Surg 98(2):269-272.

Handel N, Cordray T, Gutierrez J and Jensen J A (2006), A long-term study of outcomes, complications, and patient satisfaction with breast implants, Plast Reconstr Surg, 117, 757-767.

Heden P, Bone B, Murphy DK, Slicton A, Walker PS. (2006a) Style 410 cohesive silicone breast implants: safety and effectiveness at 5 to 9 years after implantation. Plast Reconstr Surg 118(6):1281-1287.

Heden P, Bronz G, Elberg JJ, Deraemaecker R, Murphy DK, Slicton A *et al.* (2009) Long-term safety and effectiveness of style 410 highly cohesive silicone breast implants. Aesthetic Plast Surg 33(3):430-436.

Heden P, Nava MB, van Tetering JP, Magalon G, Fourie lR, Brenner RJ *et al.* (2006b) Prevalence of rupture in inamed silicone breast implants. Plast Reconstr Surg 118(2):303-308.

Hemminki E, Hovi S L, Sevon T, and Asko-Seljavaara S (2004), Births and perinatal health of infants among women who have had silicone breast implantation in Finland, 1967-2000, *Acta Obstet Gynecol Scand*, 83, 1135-1140.

Hennekens CH, Lee IM, Cook NR, Hebert PR, Karlson EW, LaMotte F *et al.* (1996) Self-reported breast implants and connective-tissue diseases in female health professionals. A retrospective cohort study. JAMA 275(8):616-621.

Henriksen TF, Fryzek JP, Hölmich LR, McLaughlin JK, Krag C, Karlsen R *et al.* (2005) Reconstructive breast implantation after mastectomy for breast cancer: clinical outcomes in a nationwide prospective cohort study. Arch Surg 140(12):1152-1159.

Henriksen TF, Hölmich LR, Friis S, McLaughlin JK, Fryzek JP, Høyer A.P. *et al.* (2003) The danish registry for plastic surgery of the breast: establishment of a nationwide registry for prospective follow-up, quality assessment, and investigation of breast surgery. Plast Reconstr Surg 111(7):2182-2189.

Henriksen TF, Olsen JH. (2002) The Danish Registry for Plastic Surgery of the Breast; Status Report 2002. 1, 1-30. 2002. Copenhagen, Danish Registry for Plastic Surgery of the Breast.

Hochberg M C and Perlmutter D L (1996), The association of augmentation mammoplasty with connective tissue disease, including systematic sclerosis (scleroderma): a meta-analysis, Curr Top Microbiol Immunol, 210, 411-417.

Hochberg M C, Perlmutter D L, Medsger T A Jr, Nguyen K, Steen V, Weisman M H, White B and Wisley F M (1996), Lack of an association between augmentation mammoplasty and systemic sclerosis (scleroderma), Arthr Rheum, 7, 1125-1131.

Holm C, and Mühlbauer W. (1998) Toxic shock syndromein plastic surgery patients: case report and review of the literature Aesthetic Plast Surg. 22(3):180-184.

Hölmich LR, Friis S, Fryzek JP, Vejborg IM, Conrad C, Sletting S *et al.* (2003) Incidence of silicone breast implant rupture. Arch Surg 138(7):801-806.

Hölmich LR, Fryzek JP, Kjøller K, Breiting VB, Jørgensen A, Krag C *et al.* (2005) The Diagnosis of Silicone Breast-Implant Rupture: Clinical Findings Compared With Findings at Magnetic Resonance Imaging. Ann Plast Surg 54(6):583-589.

Holmich L R, Kjoller K, Fryzek J P, Hoier-Madsen M, Vejborg I, Conrad C, Sletting S, McLaughlin JK, Breiting V and Friis S (2003b), Self-reported diseases and symptoms by rupture status among unselected Danish women with cosmetic silicone breast implants, Plast Reconstr Surg, 111, 723-732.

Hölmich LR, Kjøller K, Vejborg I, Conrad C, Sletting S, McLaughlin JK *et al.* (2001) Prevalence of silicone breast implant rupture among Danish women. Plast Reconstr Surg 108(4):848-858

Hölmich L R, Mellemkjaer L, Gunnarsdottir K A, Tange U, Krag C, Meller S and McLaughlin J K (2003c), Stage of breast cancer at diagnosis among women with cosmetic breast implants, Br J Cancer, 88, 832-838.

Hölmich LR, Vejborg IM, Conrad C, Sletting S, Høier-Madsen M, Fryzek JP *et al.* (2004) Untreated silicone breast implant rupture. Plast Reconstr Surg 114(1):204-214.

Hölmich LR, Vejborg I, Conrad C, Sletting S, McLaughlin JK. (2005) The diagnosis of breast implant rupture: MRI findings compared with findings at explantation. Eur J Radiol 53(2):213-225.

Hoshaw S J, Klein P J, Clark B D, Cook R R and Perkins L L (2001), Breast implants and cancer: causation, delayed detection, and survival, Plast Reconst Surg, 107, 1393-1407.

Huang TT, Blackwell SJ, Lewis SR. (1978) Migration of silicone gel after the "squeeze technique" to rupture a contracted breast capsule. Case report. Plast Reconstr Surg 61(2):277-280.

Hvilsom G B, Holmich L R, Henriksen T F, Lipworth L, McLaughlin J K and Friis S (2009), Local complications after cosmetic breast augmentation: results from the Danish Registry for Plastic Surgery of the Breast, Plast Reconstr Surg, 124, 919-925.

Hvilsom GB, Hölmich LR, Henriksen TF, Lipworth L, McLaughlin JK, Friis S. (2010) Local complications after cosmetic surgery: results from tehDanish Registry for Plastic Surgery of the Breast Plast Surg Nurs. 30(3):172-179.

Independent Review Group (1998), Silicone Gel Breast Implants: the Report of the Independent Review Group, Cambridge, England, Crown.

Ikeda DM, Borofsky HB, Herfkens RJ, Sawer-Glover AM, Birdwell RL, Glover GH. (2000) Silicone Breast Implant Rupture: Pitfalls of Magnetic Resonance Imaging and Relative

Efficacies of Magnetic Resonance, Mammography and Ultrasound. Plast Reconstr Surg 104(7):2054-2055

International Agency for Research on Cancer (1999), Surgical implants and other foreign bodies. IARC Monograph on the Evaluation of Carcinogenic Risks to Humans, Volume 74, Lyon, IARC Press

Jacobsen P H, Hölmich L R, McLaughlin J K, Olsen J, Johansen C, Kjoller K and Friis S (2004), Mortality and suicide among Danish women with cosmetic breast implants, Arch Intern Med, 164, 2450-2455

Jacobsen P H, Hölmich L R, McLaughlin J K, Olsen J, Johansen C, Kjoller K and Friis S (2004), Mortality and suicide among Danish women with cosmetic breast implants, Arch Intern Med, 164, 2450-2455

Janowsky EC, Kupper LL, Hulka BS. (2000) Meta-analyses of the relation between silicone breast implants and the risk of connective-tissue diseases. N Engl J Med 342(11):781-790.

Jensen B, Bliddal H, Kjoller K, Wittrup H, Friis S, Hoier-Madsen M, Rogind H, McLaughlin J K, Lipworth L, Danneskiold-Samsoe B and Olsend J H(2001a), Rheumatic manifestations in Danish women with silicone breast implants, Clin Rheumatol, 20, 345-352.

Jensen B, Kjoller K, McLaughlin JK, Danneskiold-Samsoe B, Bliddal H, Blot W J and Olsen J H (2001b), Muscular rheumatism following breast surgery in Denmark, Clin Exp Rheumatol, 19, 229.

Jewell M, Spear S L, Largent J, Oefelein M G, Adams W P Jr (2011), Anaplastic large T-cell lymphoma and breast implants: a review of the literature, Plast Reconstr Surg, 128, 651-661.

Kallenberg C G (1994), Overlapping syndromes, undifferentiated connective tissue disease and other fibrosing conditions, Curr Opin Rheumatol, 6, 650-654.

Karlson EW, Lee IM, Cook NR, Buring JE, Hennekens CH, Bloch KJ. (2001) Serologic evaluations of women exposed to breast implants. J Rheumatol 28(7):1523-1530.

Karlson E W, Lee I M, Cook N R, Manson J E, Buring J E and Hennekens C H (1999), Comparison of self-reported diagnosis of connective tissue disease with medical records in female health professionals: the Women's Health Cohort Study, Am J Epidemiol, 150, 652-660.

Keech J A Jr and Creech B J (1997), Anaplastic T-cell lymphoma in proximity to a saline-filled breast implant, Plast Reconstr Surg, 100, 554-555.

Keramidas E (2009) Zero breast implants infection rate and 0.05% hematoma rate following 1720 silicone implant placements for primary breast augmentation: surgical technique or surgeon luck? Aesthetic Plast Surg. 33(1):123-124.

Kern K A, Flannery J T and Kuehn P G (1997), Carcinogenic potential of silicone breast implants: a Connecticut statewide study, Plast Reconstr Surg, 100, 737-747

Kim B, Roth C, Chung K C, Young V L, van Busum K, Schnyer C and Mattke S (2011b), Anaplastic large cell lymphoma and breast implants: a systematic review. Plast Reconstr Surg, 127, 2141-2150.

Kim B, Roth C, Young V L, Chung K C, van Busum K, Schnyer C and Mattke S (2011a), Anaplastic large cell lymphoma and breast implants: results from a structured expert consultation, Plast Reconstr Surg, 128, 629-639.

Kjoller K, Friis S, Mellemkjaer L, McLauglin J K, Winther J F, Lipworth L, Blot W J, Fryzek J and Olsen J H (2001), Connective tissue disease and other rheumatic conditions following cosmetic breast implantation in Denmark, Arch Intern Med, 161, 973-979.

Kjoller K, Friis S, Signorello L B, McLaughlin J K, Blot W J, Lipworth L, Mellemkjaer L, Winther J F and Olsen J H (2002a), Health outcomes in offspring of Danish mothers with cosmetic breast implants, Ann Plast Surg, 48, 238-245.

Kjoller K, Holmich L R, Jacobsen P H, Friis S, Fryzek J, McLaughlin J K, Lipworth L, Henriksen T F, Jørgensen S, Bittmann S and Olsen J H (2002b), Epidemiological investigation of local complications after cosmetic breast implant surgery in Denmark, Ann Plast Surg, 48, 229-237.

Kjoller K, Hölmich LR, Fryzek J P, Jacobsen P H, Friis S, McLaughlin J K, Lipworth L, Henriksen T F, Jorgensen S, Bittmann S and Olsen J H (2003), Characteristics of women with cosmetic breast implants compared with women with other types of cosmetic surgery and population-based controls in Denmark, Ann Plast Surg, 50, 6-12

Kjoller K, McLaughlin J K, Friis S, Blot W J, Mellemkjaer L, Hogsted C, Winther J F and Olsen J H (1998), Health outcomes in offspring of mothers with breast implants, Pediatrics, 102, 1112-1115.

Kulmala I, McLaughlin J K, Pakkanen M, Lassila K, Holmich L R, Lipworth L, Boice J D, Raitanen J and Luoto R (2004), Local complications after cosmetic breast implant surgery in Finland, Ann Plast Surg, 53, 413-419.

Lahiri A, Waters R. (2006) Locoregional silicone spread after high cohesive gel silicone implant rupture. J Plast Reconstr Aesthet Surg 59(8):885-886.

Lai S, Goldman J A, Child A H, Engel A and Lamm S H (2000), Fibromyalgia, hypermobility, and breast implants, Rheumatol, 27, 2237-2241.

Laing T J, Gillepsie B W, Lacey J V, Garabrant D H, Cooper B C, Heeringa S G, Alcer K H, Cho S, Mayes M D and Schottenfeld D (1996), The association between silicone exposure and undifferentiated connective tissue disease among women in Michigan and Ohio, Arthr Rheum, 39, S150.

Laing T J, Schottenfeld D, Lacey J V, Gillespie B W, Garabrant D H, Cooper B C, Heeringa S G, Alcser K H and Mayes M D (2001), Potential risk factors for undifferentiated connective tissue disease among women: implanted medical devices, Am J Epidemiol 2001154, 610-617.

Lamm S H (1998), Silicone breast implants, breast cancer and specific connective tissue diseases: A systematic review of the data in the epidemiological literature, Int J Toxicol, 17, 497-527.

Lane T, Curtis J. (2005) Reports of "dissolving" shells of silicone gel-filled breast implants. Plast Reconstr Surg 115(5):1442-1445.

Lee I M, Cook N R, Shadick N A, Pereira E and Buring J E (2010), Prospective cohort study of breast implants and the risk of connective tissue diseases, Int J Epidemiol, 40, 230-238.

Leibman AJ, Kossoff MB, Kruse BD. (1992) Intraductal extension of silicone from a ruptured breast implant. Plast Reconstr Surg 89(3):546-547.

Levine J J and Ilowite N T (1994), Sclerodermalike esophageal disease in children breast-fed by mothers with silicone breast implants, JAMA 1994, 271(3), 213-216.

Levine J J, Ilowite N T, Pettei M J and Trachtman H (1996a), Increased urinary NO3(-) + NO2- and neopterin excretion in children breast fed by mothers with silicone breast implants: evidence for macrophage activation, J Rheumatol, 23, 1083-1087.

Levine J J, Lin H C, Rowley M, Cook A, Teuber S S and Ilowite N T (1996b), Lack of autoantibody expression in children born to mothers with silicone breast implants, Pediatrics, 97, 243-245.

Levine J J, Trachtman H, Gold D M and Pettei M J (1996c), Esophageal dysmobility in children breast-fed by mothers with silicone breast implants. Long-term follow-up and response to treatment, Dig Dis Sci, 4, 1600-1603.

Lewin S L and Miller T A (1997), A review of epidemiologic studies analyzing the relationship between breast implants and connective tissue diseases, Plast Reconstr Surg, 100, 1309-1313.

Lienhart A, Auroy Y, Pequignot F, Benhamou D, Warszawski J, Bovet M, Jougla E. (2006) Survey of anesthesia-related mortality in France. Anesthesiology 105(6);1087-1097.

Lipworth L, Holmich, L R and McLaughlin J K (2010a), Silicone breast implants and connective tissue disease: no association, Semin Immunopathol, 33, 287-294.

Lipworth L and McLaughlin J K (2010), Excess suicide risk and other external causes of death among women with cosmetic breast implants: a neglected research priority, Curr Psychiatry Rep, 12, 234-238

Lipworth L, Nyren O, Ye W, Fryzek J P, Tarone R E and McLaughlin J K (2007), Excess mortality from suicide and other external causes of death among women with cosmetic breast implants, Ann Plast Surg, 59, 119-123

Lipworth L, Tarone R E, Friis S, Ye W, Olsen J H, Nyren O and McLaughlin J K (2008), Cancer among Scandinavian women with cosmetic breast implants: a pooled long-term follow-up study, Int J Cancer, 124, 490-493

Lipworth L, Tarone R E and McLaughlin J K (2004a), Breast implants and fibromyalgia: a review of the epidemiologic evidence, Ann Plast Surg, 52, 284-287.

Lipworth L, Tarone R E and McLaughlin J K (2004b), Silicone breast implants and connective tissue disease: an updated review of the epidemiologic evidence, Ann Plast Surg, 52, 598-601.

Lipworth L, Tarone R E and McLaughlin J K (2009), Breast implants and lymphoma risk: a review of the epidemiologic evidence through 2008, Plast Reconstr Surg, 123: 790-793.

Maharaj SV (2004) Platinum concentration in silicone breast implant material and capsular tissue by ICP-MS Anal. Bioanal. Chem 380 (2004) 84-89

Malata CM, Varma S, Scott M, Liston JC, Sharpe DT. (1994) Silicone breast implant rupture: common/serious complication? Med Prog Technol 20(3-4):251-260.

Males S, Joly V, Adle-Biasssette H, Abgrall S, Lariven S, leboulanger N, Yeni P (2010) Silicone in HIV-1 infected patients: a cause of misdiagnosed granulomatous disease. . Int J Infet Dis 2010 Suppl 3:e277-279. Epub 2010 Mar 20.

Malone K E, Stanford J L, Daling J R and Voigt L F (1992), Implants and breast cancer, Lancet, 339, 1365

Marotta JS, Goldberg EP, Habal MB, Amery DP, Martin PJ, Urbaniak DJ *et al.*(2002) Silicone Gel Breast Implant Failure: Evaluation of Properties of Shells and Gels for Explanted Prostheses and Meta-analysis of Literature Rupture Data. Ann Plast Surg 49(3):227-247.

Marotta JS, Widenhouse CW, Habal MB, Goldberg EP. (1999) Silicone gel breast implant failure and frequency of additional surgeries: analysis of 35 studies reporting examination of more than 8,000 explants. J Biomed Mater Res 48(3):354-364.

Malyon AD, Dunn R, Weiler-Mithoff EM. (2001) Expanding silicone granuloma. Br J Plast Surg 54(3):257-259.

McCarthy CM, Pusic AL, Kerrigan CL. (2008) Silicone breast implants and magnetic resonance imaging screening for rupture: do U.S. Food and Drug Administration recommendations reflect an evidence-based practice approach to patient care? Plast Reconstr Surg 121(4):1127-1134.

McConnell JP, Moyer TP, Nixon DE, Schnur PL, Salomao DR, Crotty TB *et al.* (1997) Determination of silicon in breast and capsular tissue from patients with breast implants performed by inductively coupled plasma emission spectroscopy. Comparison with tissue histology. Am J Clin Pathol 107(2):236-246.

McLaughlin J K and Lipworth L (2004), Brain cancer and cosmetic breast implants: A review of the epidemiologic evidence, Ann Plast Surg, 52, 115-117

McLaughlin J K, Lipworth L, Fryzek J P, Ye W, Tarone R E and Nyren O (2006), Long-term cancer risk among Swedish women with cosmetic breast implants: an update of a nationwide study, J Natl Cancer Inst, 98, 557-560

McLaughlin J K, Lipworth L, Murphy D K and Walker P S (2007), The safety of silicone gel-filled breast implants: a review of the epidemiologic evidence, Ann Plast Surg, 59, 569-580

McLaughlin J K, Nyren O, Blot W J, Yin L, Josefsson S, Fraumeni J F Jr and Adami H O (1998), Cancer risk among women with cosmetic breast implants: a population-based cohort study in Sweden, J Natl Cancer Inst, 90, 156-158

Mellemkjaer L, Kjoller K, Friis S, McLaughlin J K, Hogsted C, Winther J F, Breiting V, Krag C, Kjaer S K, Blot W J and Olsen J H (2000), Cancer occurrence after cosmetic breast implantation in Denmark, Int J Cancer, 88, 301-306

Melmed E P (1998), A review of explantation in 240 symptomatic women: a description of explantation and capsulectomy with reconstruction using a periareolar technique, Plast Reconstr Surg, 101, 1364-1373.

Middleton MS. (1998) Magnetic resonance evaluation of breast implants and soft-tissue silicone. Top Magn Reson Imaging 9(2):92-137.

Miglioretti D L, Rutter C M, Geller B M, Cutter G, Barlow W E, Rosenberg R, Weaver D L, Taplin S H, Ballard-Barbash R, Carney P A, Yankaskas B C and Kerlikowske K, (2004), Effect of breast augmentation on the accuracy of mammography and cancer characteristics, JAMA, 291, 442-450.

Morgan DE, Kenney PJ, Meeks MC, Pile NS. (1996) MR imaging of breast implants and their complications. AJR Am J Roentgenol 167(5):1271-1275.

National Institutes of Health, (2005). Breast implants: status of research at the National Institutes of Health. Available from: http://orwh.od.nih.gov/pubs/rev305breastimplantsreport.pdf [Accessed June 20, 2011]

Newman M K, Zemmel M J, Bandak A Z and Kaplan B J (2006), Primary breast lymphoma in a patient with silicone breast implants: a case report and review of the literature, J Plast Reconstr Aesthet Surg, 61, 822-824.

Nyrén O, Yin L, Josefsson S, McLaughlin JK, Blot WJ, Engqvist M *et al.* (1998a) Risk of connective tissue disease and related disorders among women with breast implants: a nation-wide retrospective cohort study in Sweden. BMJ 316(7129):417-422.

Pajkos A, Deva AK, Vickery K, Cope C, Chang L, Cossart YE. (2003) Detection of subclinical infection in significant breast implant capsules. Plast Reconstr Surg. 111(5):1605-1611.

Park A J, Black R J, Sarhadi N S, Chetty U and Watson A C (1998a), Silicone gel-filled breast implants and connective tissue diseases, Plast Reconstr Surg, 101, 261-268.

Park A J, Chetty U and Watson A C (1998), Silicone breast implants and breast cancer, Breast, 7, 22-26

Peters W, Keystone E, Smith D. (1994) Factors affecting the rupture of silicone-gel breast implants. Ann Plast Surg 32(5):449-451.

Peters W, Smith D, Fornasier V, Lugowski S, Ibanez D. (1997) An Outcome Analysis of 100 Women After Explantation of Silicone Gel Breast Implants. Ann Plast Surg 39(1):9-19.

Peters W, Smith D, Lugowski S. (1999) The life span of silicone gel breast implants and a comparison of mammography, ultrasonography, and magnetic resonance imaging in detecting implant rupture: a meta-analysis [letter; comment]. Ann Plast Surg 43(1):97-99.

Peters W, Smith D, Lugowski S, McHugh A, MacDonald P, Baines C. (1996) Silicon and silicone levels in patients with silicone implants. Curr Top Microbiol Immunol 210:39-48.

Phillips JW, de Camara DL, Lockwood MD, Grebner WC. (1996) Strength of silicone breast implants. Plast Reconstr Surg 97(6):1215-1225.

Pittet B, Montandon B, Pittet D (2005) Infection inbreast implants. Lancet Infect Dis 5(2):94-106.

Placik O J (1994), Re: Sclerodermalike esophageal disease in children of mothers with silicone breast implants (letter), JAMA, 272), 768-769.

Press R I, Peebles C L, Kumagai Y, Ochs R L and Tan E M (1992), Antinuclear autoantibodies in women with silicone breast implants, Lancet, 340, 1304-1307.

Pukkala E, Boice J D Jr, Hovi S L, Hemminki E, Asko-Seljavaara S, Keskimaki I, McLaughlin J K, Pakkanen M, Teppo L (2002), Incidence of breast and other cancers among Finnish women with cosmetic breast implants, 1970-1999, J Long Term Eff Med Implants, 12, 271-279

Pukkala E, Kulmala I, Hovi S L, Hemminki E, Keskimäki I, Lipworth L, Boice J D Jr and McLaughlin J K (2003), Causes of death among Finnish women with cosmetic breast implants, 1971-2001, Ann Plast Surg, 51, 339-342

Quinn SF, Neubauer NM, Sheley RC, Demlow TA, Szumowski J. (1996) MR imaging of silicone breast implants: evaluation of prospective and retrospective interpretations and interobserver agreement. J Magn Reson Imaging 6(1):213-218.

Radovanovic Z, Radovanovic D, Golubovic A, Ivkovic-Kapicl T, Bokorov B, Mandic A. (2010) Early complications after nipple sparing mastectomy and immediate breast reconstruction with silicone prostheses: results of 214 procedures. Scand J Surg 00(3), 115-118.

Rapaport DP, Stadelmann WK, Greenwald DP. (1997) Incidence and natural history of saline-filled breast implant deflations: comparison of blunt-tipped versus cutting and tapered needles. Plast Reconstr Surg 100(4):1028-1032.

Richardson DC, Long MC, Schroeder LW, Kisielewski RW. (2002) An in vitro study of the effect of in-folds on the durability of mammary implants. J Long Term Eff Med Implants 12(4):281-297.

Robinson OGJ, Bradley EL, Wilson DS. (1995) Analysis of explanted silicone implants: a report of 300 patients. Ann Plast Surg 34(1):1-6.

Rohrich RJ, Adams WPJ, Beran SJ, Rathakrishnan R, Griffin J, Robinson JBJ *et al.* (1998) An analysis of silicone gel-filled breast implants: diagnosis and failure rates. Plast Reconstr Surg 102(7):2304-2308.

Safvi A (2000) Linguine sign. Radiology 216, 838-839.

Sahoo S, Rosen P P, Feddersen R M, Viswanatha D S, Clark D A and Chadburn A (2003), Anaplastic large cell lymphoma arising in a silicone breast implant capsule: a case report and review of the literature, Arch Pathol Lab Med, 127, e115-e118.

Sanchez-Guerrero J, Colditz GA, Karlson EW, Hunter DJ, Speizer FE, Liang MH. (1995) Silicone breast implants and the risk of connective-tissue diseases and symptoms. N Engl J Med 332(25):1666-1670.

Sarwer D B, LaRossa D, Bartlett S P, Low D W, Bucky L P and Whitaker L A (2003), Body image concerns of breast augmentation patients, Plast Reconstr Surg, 112, 83-90

Sarwer D B, Nordmann J E and Herbert J D (2000), Cosmetic breast augmentation surgery: a critical overview, J Womens Health Gend Based Med, 9, 843-856

Schnur PL, Weinzweig J, Harris JB, Moyer TP, Petty PM, Nixon D *et al.* (1996) Silicon analysis of breast and periprosthetic capsular tissue from patients with saline or silicone gel breast implants. Plast Reconstr Surg 98(5):798-803.

Schusterman M A, Kroll S S, Reece G P, Miller M J, Ainslie N, Halabi S and Balch C M (1993), Incidence of autoimmune disease in patients after breast reconstruction with silicone gel implants versus autogenous tissue: A preliminary report, Ann Plast Surg, 31, 1-6.

Shaaban H, Jmor S, Alvi R. (2003) Leakage and silicone lymphadenopathy with cohesive breast implant. Br J Plast Surg 56(5):518-519.

Siggelkow W, Klosterhalfen B, Klinge U, Rath W, Faridi A. (2004) analysis of local complications following explantationof silicone breast implants Breast. 13(2):122-8.

Signorello L B, Fryzek J P, Blot W J, McLaughlin J K and Nyren O (2001), Offspring health risk after cosmetic breast implantation in Sweden, Ann Plast Surg, 46, 279-286.

Silman A J and Hochberg M C (2001), Epidemiology of rheumatic diseases. Second edition, New York, Oxford University Press.

Silverman B G, Brown S L, Bright R A, Kaczmarek R G, Arrowsmith-Lowe J B and Kessler D A (1996), Reported complications of silicone gel breast implants: an epidemiologic review, Ann Intern Med, 124, 744-756.

Silverstein M J, Gierson E D, Gamagami P, Handel N and Waisman J R (1990), Breast cancer diagnosis and prognosis in women augmented with silicone gel-filled implants. Cancer, 66, 97-101.

Silverstein M J, Handel N, Gamagami P, Gierson E D, Furmanski M, Collins A R, Epstein M, and Cohlan B F (1992), Breast cancer diagnosis and prognosis in women following augmentation with silicone gel-filled prostheses, Eur J Cancer, 28, 635-640.

Silverstein M J, Handel N, Gamagami P, Waisman J R, Gierson E D, Rosser R J, Steyskal R and Colburn W (1988), Breast cancer in women after augmentation mammoplasty, Arch Surg, 123(6), 681-685

Slavin S A and Goldwyn R M (1995), Silicone gel implant explantation: reasons, results, and admonitions, Plast Reconstr Surg, 95, 63-66.

Solomon G (1994), A clinical and laboratory profile of symptomatic women with silicone breast implants, Semin Arthritis Rheum, 24, 29-37.

Song JW, Kim HM, Bellfi LT, Chung KC. (2011) The effect of study design biases on the diagnostic accuracy of magnetic resonance imaging for detecting silicone breast implant ruptures: a meta-analysis. Plast Reconstr Surg 127(3):1029-1044.

Soo MS, Kornguth PJ, Walsh R, Elenberger C, Georgiade GS, DeLong D *et al.* (1997) Intracapsular implant rupture: MR findings of incomplete shell collapse. J Magn Reson Imaging 7(4):724-730.

Spear SL, Murphy DK, Slicton A, Walker PS (2007). Inamed silicone breast implant core study results at 6 years. Plast Reconstr Surg 120(7 Suppl 1):8S-16S.

Strom B L, Reidenberg M M, Freundlich B and Schinnar R (1994), Breast silicone implants and risk of systemic lupus erythematosus, J Clin Epidemiol, 47, 1211-1214.

Taylor RB, Eldred DE, Kim G, Curtis JM, Brandon HJ, Klykken PC. (2007) Assessment of silicone gel breast implant biodurability by NMR and EDS techniques. J Biomed Mater Res A.

Teuber S S and Gershwin M E (1994), Autoantibodies and clinical rheumatic complaints in two children of women with silicone breast implants, Int Arch Allergy Immunol, 103, 105-108.

Teuber SS, Reilly DA, Howell L, Oide C, Gershwin ME. (1999) Severe migratory granulomatous reactions to silicone gel in 3 patients. J Rheumatol 26(3):699-704.

Tugwell P, Wells G, Peterson J, Welch V, Page J, Davison C *et al.* (2001) Do silicone breast implants cause rheumatologic disorders? A systematic review for a court-appointed national science panel. Arthritis Rheum 44(11):2477-2484.

Van Rappard JH, Sonneveld GJ, van Twisk R, Borghouts JM. (1988) Pressure resistance of breast implants as a function of implantation time. Ann Plast Surg 21(6):566-569.

Villeneuve P J, Holowaty E J, Brisson J, Xie L, Ugnat A M, LaTulippe L and Mao Y (2006), Mortality among Canadian women with cosmetic breast implants, Am J Epidemiol, 164, 334-341

Wells KE, Cruse CW, Baker JLJ, Daniels SM, Stern RA, Newman C *et al.* (1994) The health status of women following cosmetic surgery. Plast Reconstr Surg 93(5):907-912.

Williams D. (1996) Silicon, silicone and silica: the importance of the right ending. Medical Device Technology January/February 1996, pages 7-11.

Williams H J, Weismann M H and Berry C C (1997), Breast implants in patients with differentiated and undifferentiated connective tissue disease, Arthr Rheum, 40, 437-440.

Wolf CJ, Brandon HJ, Young VL, Jerina KL.(2000) Effect of surgical insertion on the local shell properties of SILASTIC II silicone gel breast implants. J Biomater Sci Polym Ed 11(10):1007-1021.

Wolfe F (1999), "Silicone related symptoms" are common in patients with fibromyalgia: no evidence for a new disease, J Rheumatol, 26, 1172-1175.

Wolfe F and Anderson J (1999), Silicone filled breast implants and the risk of fibromyalgia and rheumatoid arthritis, J Rheumatol, 26, 2025-2028.

Wong CH, Samuel M, Tan BK, Song C. (2006) Capsular contracture in subglandular breast augmentation with textured versus smooth breast implants: a systematic review. Plast Reconstr Surg. 118(5):1224-1236.

Xie L, Brisson J, Holowaty E J, Villeneuve P J and Mao Y (2010), The influence of cosmetic breast agumentation on the stage distribution and prognosis of women subsequently diagnosed with breast cancer, Int J Cancer, 126, 2182-2190.

Young V L, Nemecek J R and Nemecek D A (1994), The efficacy of breast augmentation: breast size increase, patient satisfaction, and psychological effects, Plast Reconstr Surg, 94, 958-969

Young VL, Peters W, Brandon HJ, Jerina KL, Wolf CJ. (1998) Determining of the frequency of breast implant failure requires sound scientific principles [letter]. Plast Reconstr Surg 102(4):1295-1301.

Zambacos GJ, Nguyen D, Morris RJ. (2004) Effect of povidone iodine on silicone gel breast implants in vitro: implications for clinical practice. Plast Reconstr Surg. 114(3):706-710; discussion 711-712.