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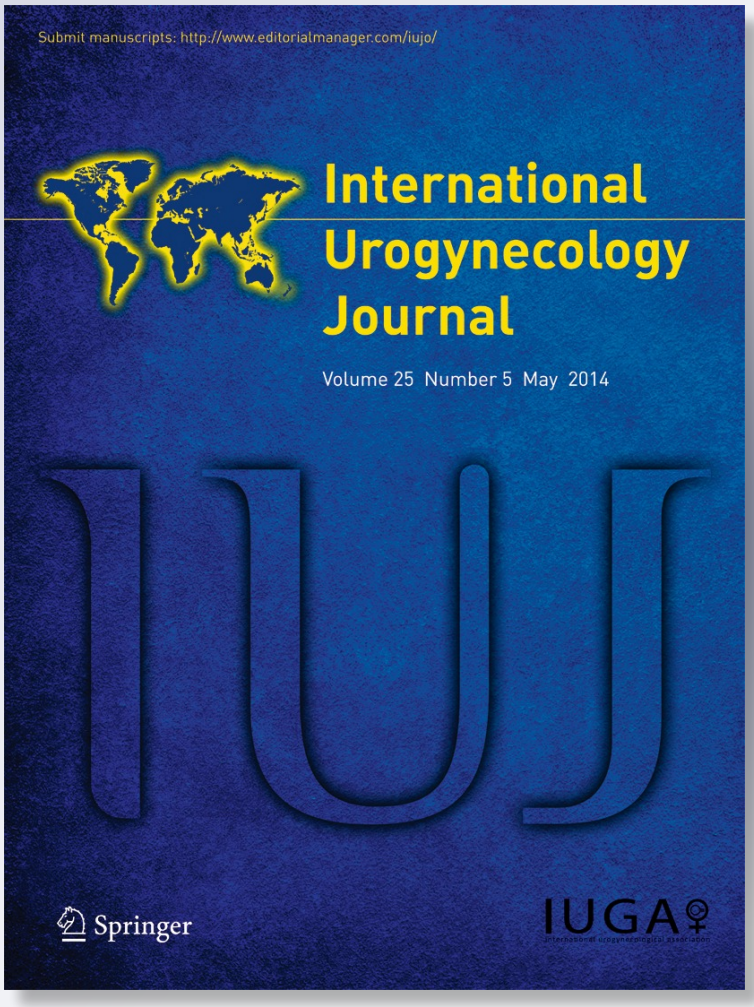

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SPECIAL CONTRIBUTION

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Abstract Recent product-liability litigation concerning polypropylene meshes has been associated with a number of claims about the suitability of these meshes for conditions such as pelvic organ prolapse (POP) surgery. It has been stated, for example, that they pose a risk for tumor formation on the basis of some animal studies that have appeared in the literature and on a few suggestions of circumstantial evidence. However, it is clear that studies of biomaterial-related tumors in animals have no relevance to clinical performance in humans. If anything, these studies predict that smooth, flat, implant surfaces are more at risk, which places polypropylene meshes in the least-risk category. Attempts to demonstrate implant-induced carcinogenicity from population studies in humans with many types of devices have routinely failed to do so.

Keywords Polypropylene · Carcinogenicity · Mesh · Animal models · Biomaterials

Introduction

Among various claims about the unsuitability of polypropylene meshes for urological and urogynecological surgery, it has been stated that the fact that polypropylene has been found "to be carcinogenic" in some laboratory animals indicates that long-term follow-up is required in all patients implanted with polypropylene meshes for urogynecological and other procedures in case carcinogenicity is eventually manifest in humans. It is extremely important that this issue is addressed seriously, as the implications for patients and physicians are potentially very serious.

The evidence put forward in support of these claims rests on four matters. First, polypropylene implants have been shown to be associated with tumors in some experimental animals under some circumstances. Second, the inflammatory response seen with polypropylene meshes is similar to that seen in some forms of tumor development. Third, in their Material Safety Data Sheet, all manufacturers of polypropylene point to evidence that the material may be associated with sarcomas in animals and advise against implantation in humans. Fourth, the International Agency for Research in Cancer (IARC) categorizes polypropylene as category 2(b), possibly carcinogenic, when implanted as smooth thin films.

We may consider the latter two points first and move on to the more serious debate. Unless they specifically and knowingly target medical markets, the majority of manufacturers of chemicals and materials add words of caution about using their materials in medical applications within their Safety Data Sheets purely in order to avoid being conjoined in litigation. There are no implications for human carcinogenicity at all with this risk-avoidance strategy. As far as IARC is concerned, many materials are placed in the potentially carcinogenic category simply because there is no hard evidence that they are not, which is very different to saying that there are causes for concern about human carcinogenicity. I was present at the IARC meeting in Lyon, France, when this matter was discussed in relation to implantable devices and, taking the most cautious approach, many materials were placed in this 2 (b) category. Materials included in this category were all polymeric implants prepared as smooth thin films [except poly(glycolic acid)], all metallic implants prepared as thin smooth films, and all implanted foreign bodies composed of metallic cobalt, metallic nickel, and one nickel–cobalt–iron

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alloy. Most materials implicitly included in this list have been used in implantable devices for decades without any hint of tumor causation. The relevance to thin smooth films is seen later in this paper, but we should note that meshes are not in this category. In a position paper relating to this report from IARC [1], McGregor et al. point to the fact that a wide range of polymers has produced sarcomas in experimental animals, such as mice and rats.

Evidence of tumors associated with implantable devices in humans

So we must turn our attention to questions of whether implantable devices in general and polypropylene meshes in particular are responsible for tumors in human patients and whether the tissue response to implanted biomaterials is indicative of potential tumorigenicity. We must be clear on some terminology issues here. Ever since tumors were found in experimental animals within the vicinity of implanted polymers [2], the phenomenon has been termed carcinogenicity. However, not all such tumors are carcinomas; they may be sarcomas, osteosarcomas, or other types. I adopt the conventional term carcinogenicity while recognizing that we must be vigilant with respect to the possibility that tumors other than carcinomas may be involved.

It has been correctly pointed out that, to date, there have been no reports of tumors associated with polypropylene meshes. It has also been correctly noted that there is likely to be a latent induction period for tumor appearance, which could be measured in years, so that in humans, a tumor-free period associated with the relatively recent history of polypropylene meshes in the treatment of pelvic organ prolapse (POP) and stress urinary incontinence (SUI) may not be that comforting. We must point out, however, that polypropylene meshes have been used for much longer in hernia repair, and there is no evidence of tumors caused by meshes here, in spite of millions of procedures performed worldwide. Two cases of squamous cell carcinomas associated with infection developing 6 and 24 years after implantation of polyester meshes for hernia repair [3] have been used as evidence to support the contention that tumors are possible; the comment of the authors of that case report paper should, however, be borne strongly in mind: "In both patients, the infection took place over a bridged polyester mesh that got infected and unincorporated. It is our impression that the mesh itself did clearly not cause it".

Ever since biomaterials were first used consistently in implantable devices, one of the generic specifications for these materials was that they should do no harm, which was often correlated with a series of negatives: they should be nonthrombogenic, nonimmunogenic … and noncarcinogenic [4]. We now have >60 years of experience with many different types of material (metals, polymers, ceramics, etc.) in many different clinical disciplines (joint replacements, prosthetic heart valves, vascular grafts, dental implants, pacemakers, intraocular lenses, etc.). I estimate the exposure of humans to implantable devices of all kinds to be more than a billion implant-years. In the more than 100 million people who have implants, one might expect a reasonable number of them to develop cancer at some stage, and statistically, one would expect that in some of these individuals, tumors would spontaneously develop tumors in the vicinity of the device; however, the evidence is to the contrary.

In the field of joint replacements, which probably represents the largest group of large implantable devices, Gillespie et al. [5] reported on an increase in lymphatic and hematopoietic cancers in hip replacement patients, but also a significant decrease in breast, colon, and rectal cancers, using an analysis of >14,000 patient-years exposure. They could not demonstrate any causation and concluded that factors other than the devices, such as drug therapy, were likely responsible. Those authors carried out another study several years later and could not confirm any correlation with these implants and hematopoietic cancers [6]. A recent study aimed at identifying increased cancer risk associated with the use of metal bearings showed that 7 years after implantation, patients had a lower risk than that predicted for the age- and sex-matched normal population [7]. Interestingly, in relation to comments about the relationship between chronic inflammation (possibly as a consequence of the presence of polypropylene implants) and tumors, Lindgren suggested that it is likely to be an underlying systemic inflammatory condition that contributes to a greater risk of lymphomas in implanted patients, those with rheumatoid arthritis being at a slightly higher risk compared with those with osteoarthritis [8]. Literature searches involving hip replacement and osteosarcomas inevitably draw attention to the use of prostheses to treat patients with cancer rather than cancer being caused by the devices.

One other type of device that should be discussed in the context of possible carcinogenicity is the breast implant. These devices are large and widely used and have been a source of speculation about a link to cancer risk, a matter that, as with polypropylene meshes, became contentious in the context of product liability litigation. It should be noted that, as with joint replacements, a recent epidemiological study showed no link between these silicone-based implants and cancer, that women with implants have no greater incidence of or death from cancer, and show no differences in post-breast-cancer survival than controls [9]. This should also be put into the context that some forms of breast implants popular in the 1980s had a surface layer of polyurethane on the silicone shell that contained a component that was possibly carcinogenic in animals. This component was toluene diamine (TDA), which could be released as a result of degradation of this polyurethane derived from toluene diisocyanate (TDI). Scientific

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studies showed that the risk of cancer associated with this release was around one case per one million women; no significant numbers of tumors were found clinically [10].

One further example of the release of a potentially carcinogenic agent into tissues from an implanted device that failed to produce tumors in humans is provided by the experience with Trilucent™ breast implants. These implants were introduced into the market in Europe following regulatory disapproval of silicone-gel-based implants. An alternative filler consisting of polyunsaturated fatty acids was contained in a standard silicone elastomer shell; however, because lipids tend to degrade this shell, some of the filler was released into the tissue during the first few years. These fatty acids, when exposed to tissue fluids, can undergo auto-oxidation, or lipid peroxidation, which leads to the formation of aldehydes such as malondialdehyde (MDA), which is potentially both mutagenic and carcinogenic in animals. A thorough investigation of the potential risk was published in 2009 [11] that showed that although some peroxidation did take place and some MDA-DNA adducts were located in capsular macrophages and fibroblasts, there was no evidence of any local or systemic markers of cancer, and no patient in the study developed any tumors 4 years after the end of the study. Of importance here is the fact that inflammatory and reparative tissue-capsule cells are not progenitors of breast carcinoma.

There are, of course, many potential confounding factors when seeking retrospective evidence of carcinogenicity causation related to implants. Few patients are followed up rigorously, and there may be little chance of detecting such correlations. Also, many patients who receive implants have comorbidities and are on drug regimes that may influence, one way or another, cancer progression. We cannot avoid the conclusion, however, that there is no evidence that implantable devices cause cancer in humans.

Mechanistic aspects of foreign-body-related carcinogenicity

Turning now to mechanistic aspects: It has rightly been pointed out that experimental evidence indicates some carcinogenic role for both species specificity and material-device characteristics. It is necessary to examine these roles more carefully. The history of so-called solid-state carcinogenicity goes back to the early 1940s and reports of tumors that developed in rats around discs of thermoplastic materials such as phenolformaldehyde. Many experimental studies with other materials were performed over the next ~30 years, especially by the Oppenheimer and Brand groups. My colleagues Meachim and Pedley [12] and I reviewed all this work in the early 1980s and concluded the following;

> Very many materials, metallic and nonmetallic, will induce tumors in rats and mice if implanted in an appropriate physical form and size, a single, solid, nonperforated structure being the most causative. This effect occurs regardless of the chemical composition of the implant and is unrelated to the chemical released from it. The effect appears to be dose dependent, with tumor incidence being higher from larger compared with smaller implants of the same material. In the case of inert powders, particle size may be a crucial factor. Some materials, such as metal particles, also have the ability to induce experimental tumors by releasing chemical solutes.

The validity of these conclusions has not changed. Some 15 years ago, working with a different group on the morphology of preneoplastic changes associated with biomaterials subcutaneously implanted in Fischer rats, we found that all biomaterials tested produced sarcomas in between 20 % and 40 % of animals by 2 years [13]. It is true that inflammation is seen around implanted materials, and often this has some degree of chronicity. However, in the absence of infection or other confounding factors, there is no evidence that the inflammatory nature of the host response to implanted biomaterials is a causative factor in tumor formation.

The use of animals to assess biocompatibility phenomena is widespread; it forms a natural component of the preclinical testing of biomaterials and devices before they are released into the market for use in humans. After >40 years studying biocompatibility, however, I conclude that such tests are rarely predictive of performance in humans. There are many examples in which animal studies are highly misleading with respect to clinical safety and efficacy in humans. Nowhere is this seen more vividly than with carcinogenicity, where species specificity considerations mean that extrapolation from observations of tumors around biomaterials in rats and mice to clinical use in humans is scientifically invalid.

Conclusions

Concerns about polypropylene mesh carcinogenicity are misplaced. Studies on biomaterial-related tumors in animals have no relevance to clinical performance in humans. Attempts to demonstrate implant-induced carcinogenicity from population studies in humans have routinely failed to do so; indeed, devices implanted clinically that could be considered to have the potential to release mutagenic or carcinogenic substances do not exert such effects in humans. If animal studies have any relevance, it is their prediction that smooth, flat implant surfaces are a higher risk, which places polypropylene meshes in the least-risk category. The suggested need to conduct long-term follow-up on all patients with mesh

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implants because of their putative carcinogenicity should play no role in patient management.

Conflicts of interest Dr. Williams has given testimony in litigation concerning implantable meshes in urological and urogynecological surgery.

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