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Polypropylene mesh: evidence for lack of carcinogenicity

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Abstract

Tumors related to the implantation of surgical grade polypropylene in humans have never been reported. In this commentary we present a balanced review of the information on what is known regarding the host response to polypropylene and provide data as to why the potential for carcinogenicity of polypropylene mesh is exceedingly small.

Keywords

Surgical mesh; Polypropylene; Neoplasms; Material safety data sheet

Introduction

The possibility that biomaterial prosthetic devices could cause tumors or promote tumor growth has been the focus of intensive research by both clinicians and biomaterial researchers alike based on the results of animal studies; however, causality has proved difficult to establish as tumors in humans at the site of any implanted device are, in fact, extremely rare [1, 2]. Thus, a “polypropylene carcinogenesis theory” based on the foreign

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body response is not a novel idea. Indeed, it is well known that tumor formation related to biomaterials in animals is largely dependent on the physical, not the chemical configuration of the implant, with smooth large surface areas (discs and thin sheets) being carcinogenic, and irregular disrupted surfaces (e.g., those that contain pores as in meshes) lacking significant carcinogenicity [2, 3]. Here, we present a review of the information on what is known regarding the host response to polypropylene and provide data as to why the potential for the carcinogenicity of polypropylene mesh in humans is exceedingly small.

Foreign body reaction to biomaterials and carcinogenesis

The host response to implanted materials, particularly those of synthetic or metallic origin, has been well studied. It is widely accepted that this response is an extension of the default mammalian response to tissue injury. This is to say that some degree of tissue injury will occur during surgical placement of implantable materials triggering the default sequence of mammalian wound healing including hemostasis, inflammation, proliferation, and remodeling with a final outcome of scar tissue formation that cannot be separated from the host response to implanted materials. The host response to material implantation, also known as the foreign body response, has generally been described to include seven interrelated and overlapping phases including: injury, protein adsorption, acute inflammation, chronic inflammation, foreign body reaction (FBR), granulation tissue formation, and encapsulation [4, 5]. The host response to an implanted material is an unavoidable consequence associated with its use, and the end outcome of biomaterial implantation may depend upon local or systemic factors including site of implantation, quality of the tissue at the implantation site, and patient characteristics. While the foreign body response to hernia mesh has been well described in both animals and humans, the response to vaginal meshes has only recently come under investigation. In these early studies the foreign body response to polypropylene mesh appears largely limited to the periphery of individual mesh fibers with no evidence of systemic involvement [6, 7].

Multiple types of implantable materials of both metallic and synthetic origin have been shown to possess carcinogenic potential in animal studies [8, 9]. The pathogenesis of material-associated tumors is not well understood, but most studies in animals demonstrate that the physical form of the implanted material has a greater impact upon the potential for carcinogenesis than the chemical composition. Indeed, seemingly inert materials implanted as large broad smooth surfaces (such as discs and sheets) including relatively pure metals, glasses, and polymers are most carcinogenic. These solid materials lose their carcinogenicity when implanted as powders, porous, or woven forms. This phenomenon, known as the “Oppenheimer effect,” accounts for why solid discs and thin smooth sheets of polypropylene have induced cancers in animals while polypropylene meshes have not [3, 10]. It also accounts for why the WHO statement regarding polymeric implants specifically categorizes polymers “prepared as thin smooth films are possibly carcinogenic to humans (Group 2A)” to distinguish these products from materials that are highly porous, powders or segmented, which lack significant carcinogenicity. Importantly, carcinogenesis of materials in animal model systems have been studied under long latency periods (1–3 years) that are equivalent to those observed in humans (10–30 years). Based on these animal studies, it has been proposed that a series of sequential stages are essential to the formation of material-

associated carcinogenesis: (1) cellular proliferation, (2) encapsulation of the implanted material, (3) quiescence of the tissue reaction and contact of preneoplastic cells with the implant surface, (4) maturation of preneoplastic cells, and (5) sarcomatous proliferation of such cells [9, 11, 12]. Thus, evidence, to date, suggests that the foreign body acts as a physical substrate for growth of the preneoplastic cells present at the implantation site rather than the implant acting as an initiator of the neoplastic process. In this way, the foreign body per se does not initiate the tumor.

Tumorigenesis in rodents is relatively common while humans are far less susceptible to material-associated carcinogenesis. To demonstrate the relative ease of which cancer can be induced by implantable materials/substances in rats, a surgeon published a brash paper in the *Journal of the American Medical Association* titled “Money causes cancer: ban it” [13], in which he describes an experiment in which metal coins were inserted in rats and yielded a 60 % sarcoma rate over a period of 16 months [13]. Thus, the evidence indicates that while foreign body carcinogenesis in animals is relatively common, the occurrence of neoplastic transformation in the setting of clinically implanted medical devices in humans is quite rare [14–19]. This is particularly striking when one considers both the large number of medical devices which have been implanted in humans and the tens of decades for which they have been used. Indeed, only a small number of cases of implant-associated tumors have been observed that are typically mesenchymal in origin (sarcomas) and most commonly following orthopedic implants. These cases are largely reported as single occurrences or small case series [14, 16, 17]. A number of hypotheses have been advanced regarding potential mechanisms by which such implants may support neoplastic processes, with the most common related to the generation of potentially inflammatory particulate wear debris. It should be cautioned, however, that despite multiple investigations causality has never been established. An epidemiologic study by the International Agency for Research on Cancer (IARC) in 2000 concluded that there was no evidence for tumorigenicity of metallic or synthetic implants in humans [1].

Chronic inflammation and cancer

To our knowledge, bacterial adherence to polypropylene meshes with a biofilm-induced inflammatory response, although suggested in review articles [20], remains unsubstantiated. Nevertheless, an association between mesh, chronic inflammation, and genomic instability is certainly plausible. One could easily imagine that the microenvironment around mesh implants, possibly through inflammatory mediated factors, might interfere with replication repair enzymes of nearby proliferating cells and this would be reflected experimentally in genomic instability. This hypothesis was tested in a rat model of biomaterial-induced sarcoma by Weber and colleagues who were unable to find evidence of genomic instability in either fully developed tumors or preneoplastic lesions [21]. Thus, to date, there is no evidence that genomic instability is a feature of malignant transformation in biomaterial-induced soft tissue tumors. More importantly, inflammation is a complex process and not only is critical in the initial clearing the wound of debris and necrotic/abnormal cells, but it is equally crucial for tissue remodeling and regeneration [22]. For this reason, it is shortsighted and premature to assume that inflammation related to the implantation of a bio-material will be associated with poor health outcomes.

Interpreting MSDS data

A material safety data sheet (MSDS) provides a list of information required by the Occupational Safety and Health Administration (OSHA) regarding the safety and potential hazards of a material to provide guidelines to employees working with a particular product so that it is safely handled. The MSDS includes information such as physical data (melting point, boiling point, flash point, etc.), toxicity, health effects, first aid, reactivity, storage, disposal, protective equipment, and spill-handling procedures. The MSDS for polypropylene material is provided only for this material in a pellet form by the resin manufacturer. (Raw polypropylene resin, as sold by a resin manufacturer, takes the form of a pellet or sphere prior to its subsequent processing into a finished product such as a medical device.) In this case, the MSDS would be relevant to production workers involved in early manufacturing steps such as raw material storage and fiber extrusion (a step that not only changes the form of the polypropylene, but also occurs well before the product is packaged and sterilized). Because MSDSs are often directed at as broad a range of related materials as possible and the full range of possible occupational exposure conditions, they incorporate information that may not be relevant to a particular grade, or to the conditions encountered in a finished medical device (e.g., prolapse mesh), and are specifically not intended for general consumer use or as a product design document. Thus, the various polypropylene MSDS documents related to polypropylene provide only limited information that is relevant to the selection and qualification of polypropylene resin in its raw, unfinished, and unsterilized form for a particular application. In this pellet form, generic polypropylene is not evaluated or contemplated for use in humans, or even a particular product.

In addition, many times, a product cannot be recommended for human use because the requisite testing was simply not performed due to time, expense, and lack of a defined relationship to the finished product (e.g., polypropylene resin pellet vs a polypropylene prolapse mesh), though different manufacturers may communicate that in different ways. As an example, the Total Petrochemical Technical Data Sheet for polypropylene explicitly states that “The above-mentioned product is not in compliance with the US pharmacopoeia because we did not perform the required tests” [23]. Finally, the MSDS documents may reference the induction of sarcomas by polypropylene when implanted in smooth sheets or as discs in animals. As stated above, as foreign body carcinogenesis appears to be related to the physical form and not the chemical composition of a material, and polypropylene is not utilized in urogynecologic procedures as discs or smooth sheets, there is little relevance of these aspects of the MSDS documents to polypropylene mesh implants.

Polypropylene has been used throughout the world for over five decades without evidence of carcinogenesis

To date, data extrapolated from industry and marketing documents (communication with industry sources) suggest that polypropylene has been used worldwide in hundreds of millions of humans for nearly half a century without evidence of systemic disease including cancer. Indeed, billions of packages of polypropylene suture have been sold and used since the 1970s in hundreds of varied applications throughout the body. Tens of millions of

polypropylene mesh hernia units have been sold since the 1980s. Over 3 million polypropylene midurethral slings have been sold since the mid 1990s and hundreds of thousands of transvaginal mesh units have been sold in the last 10 years. To date, no mesh site cancers have been reported. A literature search revealed only one report of tumorigenesis associated with the implantation of polymeric mesh materials (two cases) and in these the mesh material was polyester, not polypropylene [24]. Moreover, in this study, both patients had long-term chronic infection of the implanted mesh—a phenomenon that is not commonly observed in vaginally implanted meshes. We propose, therefore, that the potential for carcinogenesis of polypropylene mesh is negligible when one compares the low incidence of reports of carcinogenesis against use of polypropylene as suture and as a hernia mesh in many millions of patients since the 1950s and that the formulation of polypropylene during this period has remained largely unchanged.

Conclusion

As we learned from the silicone breast implant controversy several decades ago, publications derived from a skewed interpretation of the literature and not solid evidence based on scientific data can lead to baseless damaging media hype and unscrupulous jury awards. It would be a tragedy for women worldwide if nonscientifically based articles regarding the potential hazards of polypropylene incited a spiraling course for the best (highest success rate and minimal morbidity) surgical procedure developed to date for stress urinary incontinence simply because of liability concerns by doctors, hospitals, and manufacturers. As treating physicians, we must let science and clinical studies determine our practice. More importantly, we must align with the millions of women who have been successfully treated with mesh with absolutely no evidence of systemic complications (including cancer) and who have regained control of their quality of life.

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