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Review

From sperm to offspring: Assessing the heritable genetic consequences of paternal smoking and potential public health impacts

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ABSTRACT

Individuals who smoke generally do so with the knowledge of potential consequences to their own health. What is rarely considered are the effects of smoking on their future children. The objective of this work was to review the scientific literature on the effects of paternal smoking on sperm and assess the consequences to offspring. A literature search identified over 200 studies with relevant data in humans and animal models. The available data were reviewed to assess the weight of evidence that tobacco smoke is a human germ cell mutagen and estimate effect sizes. These results were used to model the potential increase in genetic disease burden in offspring caused by paternal smoking, with specific focus on aneuploid syndromes and intellectual disability, and the socioeconomic impacts of such an effect. The review revealed strong evidence that tobacco smoking is associated with impaired male fertility, and increases in DNA damage, aneuploidies, and mutations in sperm. Studies support that these effects are heritable and adversely impact the offspring. Our model estimates that, with even a modest 25% increase in sperm mutation frequency caused by smoke-exposure, for each generation across the global population there will be millions of smoking-induced *de novo* mutations transmitted from fathers to offspring. Furthermore, paternal smoking is estimated to contribute to 1.3 million extra cases of aneuploid pregnancies per generation. Thus, the available evidence makes a compelling case that tobacco smoke is a human germ cell mutagen with serious public health and socio-economic implications. Increased public education should be encouraged to promote abstinence from smoking, well in advance of reproduction, to minimize the transmission of harmful mutations to the next-generation.

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1. Introduction

Smoking is a major societal health problem. Tobacco smoke contains more than 4000 compounds, of which at least 70 have been identified as carcinogenic [1–4]. Although the consequences of smoking are well characterized, the vast majority of studies have focused on effects in the smoker [5], or trans-placental effects on the fetus in mothers who smoke [6]. However, there is also strong evidence that paternal preconception exposure to tobacco smoke can cause intergenerational effects through the germline [7]. This effect of paternal smoking is predominantly overlooked [8].

Inherited germline mutations may have devastating impacts in the affected offspring and significant socio-economic repercussions at the population level. It is well established from animal studies that environmental exposures can increase mutation frequencies in germ cells [9]. Accordingly, the presence of potential germ cell mutagens in the environment, such as tobacco smoke, could be contributing to the occurrence of sporadic genetic diseases in human populations through the induction of *de novo* mutations. Whole genome sequencing has enabled the unprecedented analysis of the *de novo* mutations that contribute to a variety of genetic diseases. For example, recent large-scale sequencing projects have revealed that there is a strong association between *de novo* germline mutations and sporadic neuropsychiatric disorders including schizophrenia and autism [10–15]. There is also evidence that the number of *de novo* mutations in germ cells increases with paternal age [16–18]. However, thus far there has been no effort to harness genomic tools to understand the environmental mediators of such *de novo* mutations in human cohorts.

The mutagenic effects of tobacco smoking on germ cells are not well characterized. In contrast, it is well established that tobacco smoke induces DNA damage and mutations in somatic cells (reviewed in [19,20]). Indeed, approximately 90% of lung cancers are attributed to tobacco smoking [21]. Tobacco smoke was first suggested as a possible germ cell mutagen almost four decades ago by Bridges et al. [22]. Since that time, many studies have demonstrated the mutagenic effects of tobacco smoke on the germline in humans and in rodent models. In the most recent International Agency for Research on Cancer (IARC) monograph on tobacco smoke [2] it was stated that "data suggest that smoking is likely a germ cell mutagen in humans." However, there is currently no governing agency that declares agents as human germ cell mutagens [9]. It has been argued that an IARC-type of assessment may be suitable for identifying germ cell mutagens [9]. Such an assessment would have important implications because it is estimated that approximately 800 million men worldwide smoke [23] and even more may be exposed to second-hand and third-hand smoke.

In this comprehensive review, we present the evidence (Appendix A) that first-hand smoking affects sperm function and induces heritable genetic changes in male germ cells, and discuss the impact of this genetic damage on phenotypic consequences in the offspring. Finally, we evaluate the potential socio-economic ramifications of tobacco-induced mutations and show that modest increases in global germline mutation rates caused by smoking have severe consequences.

2. Human spermatogenesis

Spermatogenesis is estimated to last >70 days in adult humans [24,25] and consists of three phases: mitotic, meiotic, and post-meiotic. Spermatogenesis begins in the seminiferous tubules of the testes with a low number of self-regenerating spermatogonial stem cells (Fig. 1). A portion of these mitotic stem cells differentiate into spermatogonia that proliferate through mitosis and are

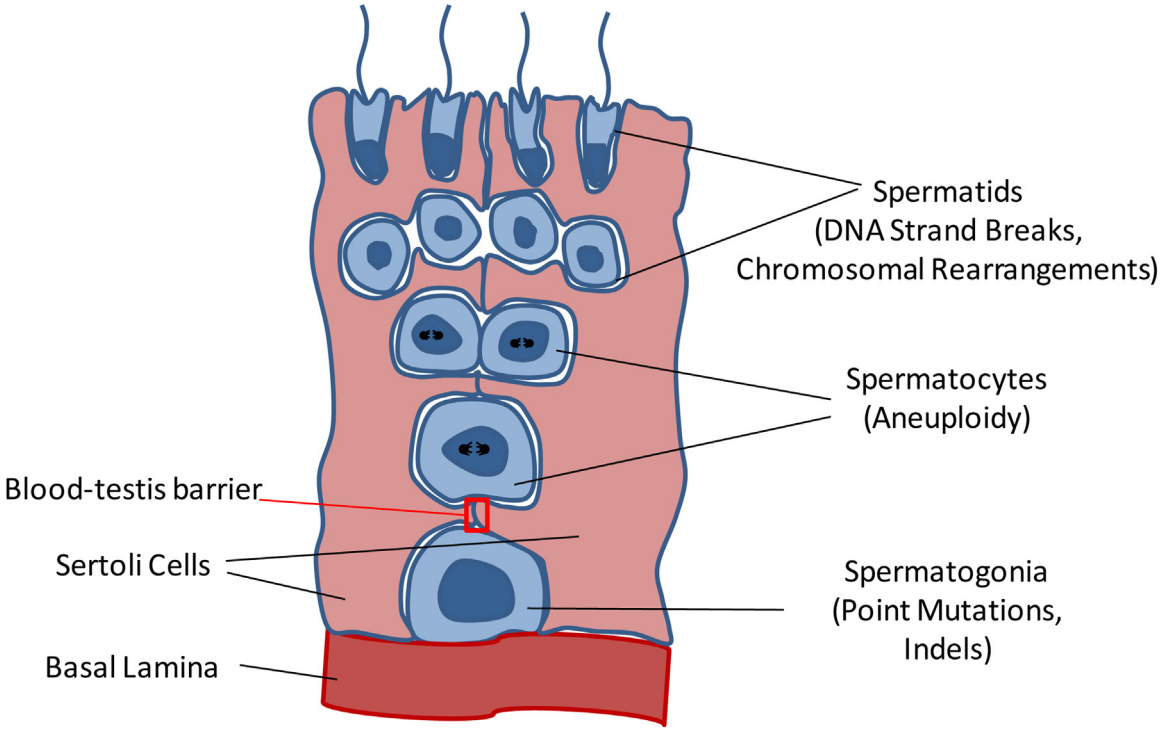

Fig. 1. Spermatogenesis and different mutations that are prevalent in the different types of sperm. Dividing spermatogonia lay on the "open" side of the blood-testis barrier formed by Sertoli cells. Mutagenic exposures typically increase the frequency of point mutations and indels in spermatogonia. Spermatocytes undergo meiotic divisions and this is the phase where aneuploidies will occur. Haploid spermatids become DNA repair deficient and therefore DNA strand breaks or damaged nucleotides go unrepaired at this stage. This can lead to inviable sperm or the induction of chromosomal rearrangements occurring post-fertilization.