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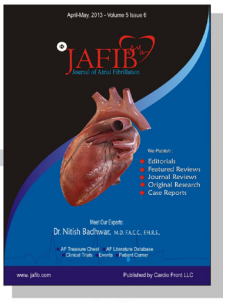

Age-Dependent Impact of Fluoroscopic Radiation on the Gender of Off-Spring: An International Survey of Cardiologists

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Abstract

Background: Fluoroscopic radiation has been implicated in reducing the sex ratio (M:F) by potentially damaging the Y chromosome. We examined the effects of exposure to fluoroscopic radiation on gender of offspring of cardiologists across the world.

Methods: An internet based survey was e-mailed worldwide to 8000 physicians who practice invasive electrophysiology and/or interventional cardiology. Survey questions included age, race, sub-specialty, hours of exposure to radiation, number of children, gender of off-spring, miscarriages and mutations and exposure to radiation prior to conception of each child. Logistic regression analyses were performed on years of exposure and gender of offspring born post radiation exposure.

Results: Responses of 377 cardiologists (84% male and 16% female) were reviewed. With a total of 398 males and 402 females born to 377 cardiologists, although reduced, the overall sex ratio (0.99) was not significantly different from that observed in the general population (1.05). Univariate logistic regression analysis identified higher male births with increasing hours of radiation exposure (OR 1.034, CI 1.003-1.067 p=0.03) and increasing paternal age (OR 1.05, CI 1.01-1.08, p=0.002). Subgroup analysis of children of male cardiologists revealed higher incidence of male births with increasing age and radiation exposure and multivariate analysis only identified paternal age as predictor of higher incidence of male births (OR 1.05, CI 1.01-1.089, p=0.0027).

Conclusion: Exposure to ionizing radiation leads to a decrease in the sex ratio (M/F) in younger male cardiologists, while this effect is reversed with greater number of male births in older male cardiologists.

Introduction

Variation in sex ratio has been a topic of debate for millennia. Sex ratio is defined as the ratio of male (M) offspring to female (F) offspring (M/F) or as a ratio of male offspring to total offspring(M/M+F)

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and stands at 1.05 (M/F) or 0.51(M/M+F) for the US population in 2005.[1] Sex ratio at birth in several countries across the world ranges from 1.02 to 1.13[2] Several large observational studies have examined the effects of maternal age, paternal age, birth order and ethnicity on reducing the sex ratio.[3-7] Environmental agents like dioxins[8,9] gasoline,[10] metal fumes and tobacco[11, 12] have also been implicated in affecting the sex ratio in favor of female offspring. Exposure of male workers to certain occupational agents has been shown to reduce the sex ratio.[8,13]

Exposure to electromagnetic radiation has been suggested to alter sex ratio in a few studies.[14-17] While some studies reported reduction in sex ratio among female physiotherapists exposed to electromagnetic radiation,[14] others did not.[18] Exposure to nuclear radiation showed an increase in sex ratio in one study[15] but others showed no such association.[19-21] Similarly, a study among male radiologists orthopedic surgeons showed a decrease in sex ratio[16, 17] whereas another study among male cardiologists exposed to fluoroscopic radiation found no change.[22]

Data from various studies on the impact of fluoroscopic radiation have been inconsistent with some obvious limitations. Study on male invasive cardiologists included only children that were born and no details on miscarriages or unborn pregnancies were noted.[22] It is unclear whether there was a difference between those born before radiation exposure vs. those born after radiation exposure[22] It is unclear from prior observations and studies if occupational exposure of toxins and radiation to men or women affects sex ratio. In addition, the interplay between the exposure to radiation and maternal and paternal age is less clear.

In the current study we examined the effects of exposure to fluoroscopic radiation and the sex ratio of offspring of male and female invasive cardiologists. We also studied the effect of duration of exposure with maternal and paternal age as well as the impact of exposure on male and female cardiologists separately.

Methods

An internet based survey in English was e-mailed worldwide to 8000 physicians who practiced invasive, electrophysiology and/or interventional cardiology. Survey questions consisted of age of the physician and the spouse, race, sub-specialty practice and hours of radiation exposure per week. The number of children born, gender of off-spring, miscarriages and mutations and duration of exposure to radiation prior to conception of each child were also queried. The results were analyzed as detailed below.

Statistical Analysis

All categorical data are presented as percentages and continuous data as means and standard deviation. A p value <0.05 was considered significant. The Z test for proportions was used to compare the sex ratio of offspring of respondents with that of the general population. Univariate and multivariate logistic regression analysis with forward approach was then performed to see if increasing years of exposure affected the gender of offspring. Maternal age, paternal age, duration of radiation exposure and birth order were considered in the analysis for all respondents and later for male and female cardiologists separately. SAS version 9.1.3 (SAS Institute Inc, Cary, NC)) was used for the analyses.

Results

Five hundred and nineteen cardiologists (84% male and 16% female) responded to the survey. Their ethnic background included 79.8% Caucasian, 15.4% Asian, 3% Hispanic, 2.4% other and 0.2% African-Americans. They included 60% electrophysiologists, 33% interventional cardiologists and 7% invasive (non-interventional) cardiologists (see table1). Of these, 58.3% were exposed to radiation (time spent in the catheterization and/or EP laboratory) on average of more than 10 hours per week, and 41.7% were exposed <10 hours per week. A total of 5.8% had exposure to other sources of radiation as well (radioactive iodine in research lab, radioactive iodine for hyperthyroidism, exposure to radiation in nuclear imaging lab), while 94.6% had exposure to fluoroscopic radiation alone.

We excluded 142 respondents who had conceived children before radiation exposure and those with incomplete surveys. All respondents (n=377) with children born only after radiation exposure were included. A total of 402 males and 403 females

Table 1 Baseline Characteristics

Mean paternal age (years)	35.7
Mean maternal age (years)	33.5
Caucasian (%)	79.8
Asian (%)	15.4
Hispanic (%)	2.4
African American (%)	0.2
Electrophysiologists (%)	60
Interventionalists (%)	33

were born to 377 physicians. Although the sex ratio in these births (0.99) was lower compared with the sex ratio of the general population (1.05), the difference did not reach statistical significance (p=0.3). The mean maternal age was 33.5 (±4.7) years and mean paternal age was 35.7 (±4.5) years. There was no difference in the maternal age (33.75 vs. 33.3 years, p = 0.2) for male and female offspring, respectively, but mean paternal age was significantly higher (36.2 vs 35.2 years, p = 0.002) for the male offspring. The majority of respondents had 2 children or more (84%) with 80 miscarriages and 27 children with genetic disorders (0.03%, 27/805). The nature of the congenital anomalies was not obtained. The total cumulative radiation exposure for male offspring was 2678 hours of radiation and total cumulative hours of radiation exposure for female offspring was 2414 hours. The mean duration of radiation exposure for the entire study sample was 6.3±4.6 years, while it was 6.7±4.8 for male offspring and 6.0 ± 4.3 for female offspring (p=0.11).

There were 46 physicians who had miscarriages only and had no children. After excluding them and another 20 male cardiologists, who did not provide their age, univariate logistic regression analysis identified higher number of male births with increasing hours of radiation exposure (OR 1.034, CI 1.003-1.067 p=0.03) and increasing paternal age (OR 1.05, CI 1.01-1.08, p=0.002). On multivariate analysis, only paternal age was associated with a greater possibility of male births (OR = 1. 05, CI 1.01-1.18, p=0.0019).

To study the effects of radiation on male and female cardiologists separately, sex ratio among the children of male cardiologists (n=266) was calculated, and found to be lower at 0.97 (M/F) with 338 males and 345 females, p=0.15 (or at 0.49 when considered as (M/M+F)) compared with the general population. Univariate analysis again identified higher male births with increasing hours of radiation exposure and increasing paternal age (See table 2). Multivariate analysis identified paternal age as the only predictor of male births (OR 1.05, CI 1.018-1.089, p=0.0027). A subgroup analysis of offspring of male cardiologists aged 37 years or more showed a significant increase in sex ratio to 1.2 (M/F) (143 males and 112 female offspring, p=0.017; M/M+F = 0.56). The sex ratio of offspring of male cardiologists aged less than 37 years was 0.84 (M/F) (196 male and 233 female offspring; M/M+F= 0.45, p=0.0009, figure 1). Offspring of female cardiologists (n=45) had a sex ratio of 1.2 (M/F) or 0.54 (M/M+F) with 45 males and 37 females (p=0.01). The sample size, however, was too small to make any meaningful prediction by regression.

Discussion

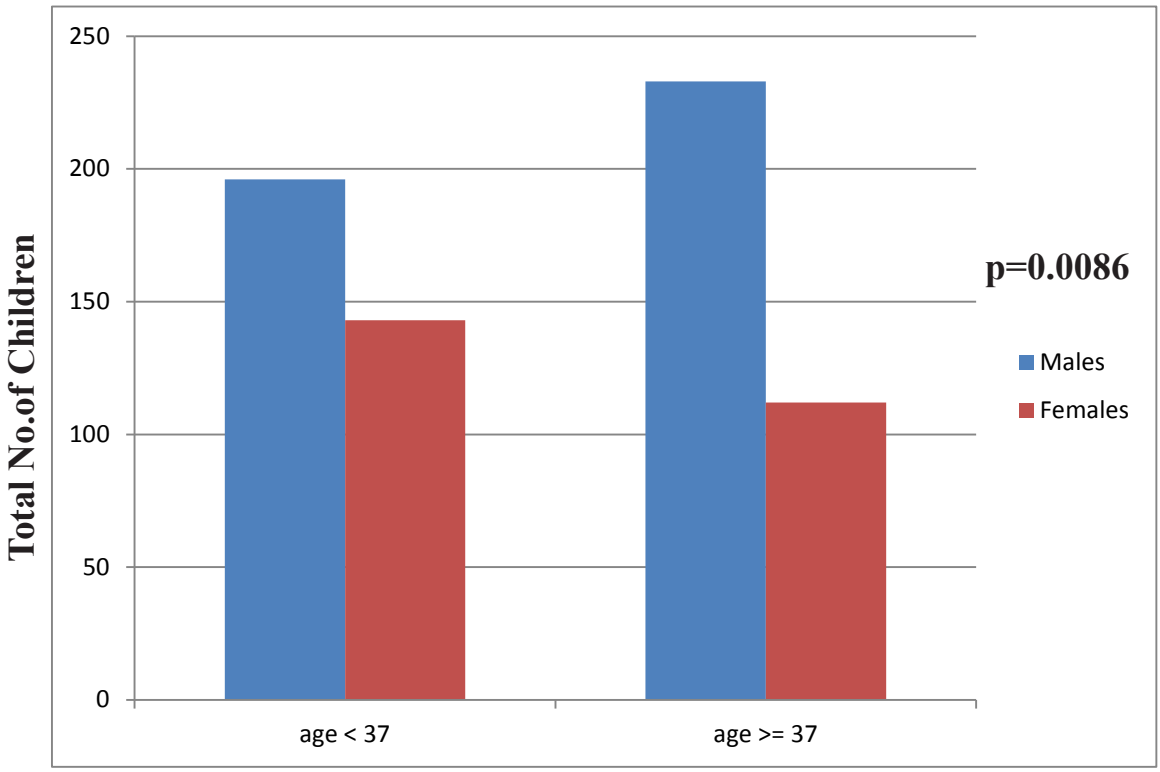
Our results show a trend toward reversal in sex ratio (lower number of male births) among the offspring of all cardiologists, especially among offspring of male cardiologists. Despite the decrease in overall number of male offspring, multivariate logistic regression analysis showed an association between increasing paternal age and higher number of male births. Offspring of female cardiologists had a higher sex ratio (greater number of male births) but the sample size was too small to make reliable interpretations. In a subgroup analysis, reduced sex ratio (0.84) was observed among offspring of male cardiologists when the paternal age was less than 37 years and a significantly increased sex ratio (1.2) was found when the paternal age was 37 years or more.

Several trials have been conducted to establish the factors predisposing to altered sex ratios, but results have been inconsistent. Our study revealed a non-significant reduction in sex ratio among all qualifying respondent cardiologists.

Table 2 Univariate Analysis Among Male Cardiologists

	Odds Ratio	CI	P value
Maternal age	1.02	0.9-1.0	0.16
Paternal age	1.053	1.01-1.089	0.0027
Duration of radiation exposure	1.032	1-1.06	0.04

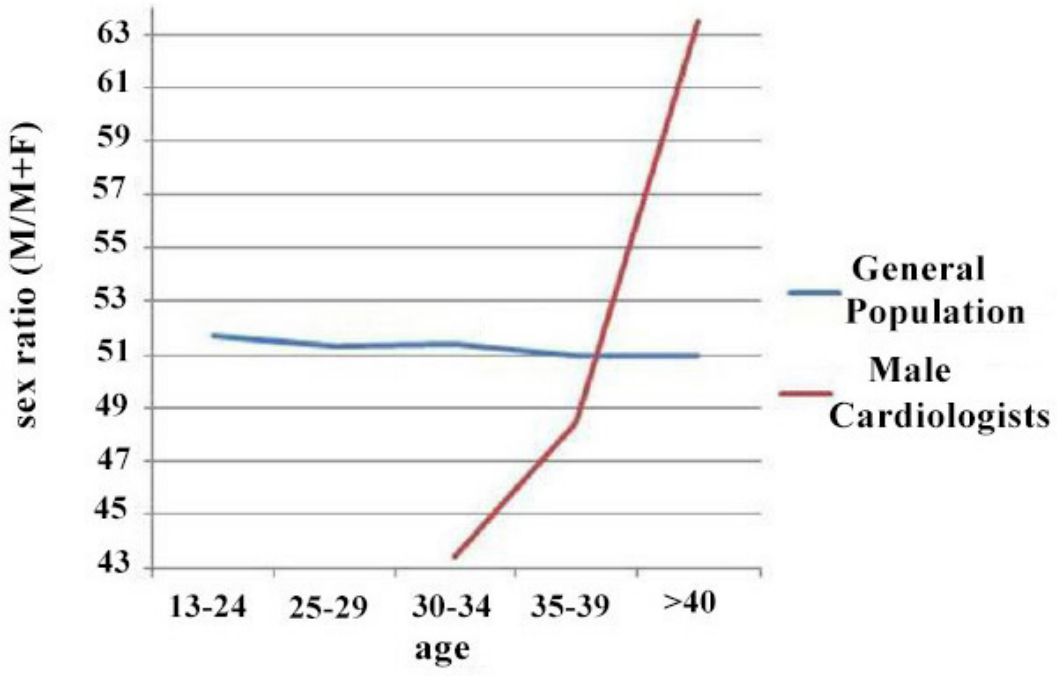
Figure 1: Sex Ratio by Male Cardiologists Age



However, when offspring of only male cardiologists were considered, a significant reduction in sex ratio was noted when the paternal age was < 37 years; and the sex ratio increased significantly when the paternal age was > 37 years. This is in stark contrast to prior larger studies which suggest a reduction in sex ratio with increasing paternal age in the unexposed general population (3, 5, 6). (figure 2 modified from data taken from the paper by Jacobsen et al. ref 5). Our study, however, showed an increase in sex ratio in cardiologists with increasing paternal age. Whether this suggests a natural variation in sex ratio in recent years, or if this is an effect of fluoroscopic radiation in cardiologists remains unknown. Nonetheless, our study results are consistent with prior findings of increased sex ratio among offspring of survivors of atomic bombing in Japan.[23] On this basis, it has been postulated that induction of sex-linked lethal mutations in germ cells would result in an increased sex ratio in the offspring of irradiated males and a decreased sex ratio in the offspring of irradiated females.[23] The single study on female physiotherapists exposed to radiation demonstrated lower sex ratio and conforms to this postulate.[14] Increased sex ratio in offspring of irradiated fathers was also seen in a few other studies.[15, 24] The current results point to an additional layer of complexity to this issue, because offspring born to younger fathers had a lower sex ratio while those born to older fathers had a higher sex ratio.

Invasive cardiologists on average are exposed to 0.01mSv to 0.02mSV of radiation per case with a higher collar level exposure despite the use of lead aprons,[25, 26] which is still less than the annual radiation exposure limit mandated by the international commission on radiological protection (< 20 m Sv /year).[27] Since the only discernible difference of these male cardiologists from the general population is exposure to fluoroscopic radiation, we postulate that the radiation is probably responsible for the change in sex ratios. Prior studies have shown increasing paternal age and birth order to have the most effect on sex ratio with a smaller effect from maternal age.[6,28] Much larger studies may be required such an effect of maternal age on sex ratio. The inability of our study to reveal any significant effects of maternal age on the sex ratio was probably related to the very small sample size. Birth order was not a predictor of sex ratio in our study because not all children born to the respondents were considered in the analysis of the birth order, rather only the children born after exposure to the radiation were considered. Duration

Figure 2: Comparison of Sex Ratio (M/M+F) of General Population and Male Cardiologists



(General Population Data is the Reference Group Derived from the Study by Jacobsen et al)

of radiation exposure also did not have an effect on the sex ratio. This could be because the natural life span of spermatozoa is only a few days, approximately 76 days[29] and exposure to radiation during the time of conception may be more important than the duration of exposure. The study on nuclear radiation workers at Sellafield, Cumbria showed that fathers exposed to more than 10mSV of radiation in the 90 days before conception produced and increased sex ratio.[15] Rate of genetic malformations due to spontaneous mutations in new born infants in a study was shown to be 0.0007% (48/69277).[30] This is significantly lower than the 0.03% rate of mutations found among cardiologists exposed to radiation in our study (P<0.0001). The incidence of genetic mutations was assessed by the survey but no confirmation or details of the same were obtained in our study.

Several hypotheses have been put forward for the variations in sex ratio in the general population with age. Some theories include reduced androgen levels in males with increasing age and reduced coital rates with older age.[31] Altered sex ratio in the radiation exposed population is explained by induction of sex linked lethal mutations in the x chromosome which are transmitted to exposed fathers daughters thereby increasing the sex ratio, whereas exposed mothers, transmit the lethal mutations to sons and thereby cause reduction in sex ratio.[23] The reduced sex ratio in our study among younger fathers remains unexplained. It is not clear if the Y-chromosome is more susceptible to the ill effects of radiation during early years of exposure resulting in higher concentration of X to Y sperm pool and thereby higher probability of female births decreasing the sex ratio in younger fathers. This effect may get blunted and the X to Y sperm pool may tilt back to normal explaining the reversal of sex ratio as the years of exposure and the paternal age increases. Chronic exposure to low levels of radiation as was with the case of older male cardiologists could have resulted in hormetic effect on the Y-chromosome of the germ cells. Radiation hormesis (also called radiation homeostasis) is the hypothesis that chronic low doses of ionizing radiation (in addition to the natural background doses) are beneficial, stimulating hypothetical reserve repair mechanisms that protect against disease, but are not activated in absence of additional ionizing radiation.[31-32] The reserve repair mechanisms are hypothesized to be sufficiently effective when stimulated as to not only cancel the detrimental effects of extra ionizing radiation but also protect from other damage.[32-35] Hormetic responses are varied in form and

include increased longevity, growth, reproductive and physiological responses and metabolic effects.

Despite this evidence of increasing sex ratio with exposure to radiation[15,23,24] several studies exist that have shown the opposite effect of decreasing sex ratio[16,17,36] or no change in ratio.[19, 21, 37] Our study is unique in that it attempts to study the gender of offspring of radiation exposed cardiologists while accounting for the maternal age, years of radiation and paternal age. Further prospective studies will be required to tease out the differences in effects of irradiation on men and women and to clearly establish the reasons for such. While controversy will continue to prevail, all cardiologists should continue to take all necessary precautions to reduce exposure to ionizing radiation to minimize general health hazards, even though it may not impact their choice of offspring gender.

Limitations

The response rate to the survey was low and hence the sample may not be representative. Radiation exposure of the spouse is not known. Our sample contained a limited number of female cardiologists. Also, only offspring born after radiation exposure were considered. The influence of birth order can be determined only if all offspring are considered. We did not measure and quantify the true radiation exposure in each participant. The amount of radiation exposure is assumed to be low underneath the lead aprons provided the integrity of these protection devices was not compromised over years of use. In reality, the exposure might have been higher than the assumed numbers.

Conclusions

Exposure to ionizing radiation seems to increase the sex ratio as paternal age increases. A higher proportion of females were born to younger fathers exposed to radiation, while a higher proportion of males were born to older fathers. The precise reason(s) for this effect is unclear and warrants further investigation.

Disclosures

No disclosures relevant to this article were made by the authors.

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