REVIEW ARTICLE:

Induced abortion as cancer risk factor: a review of epidemiological evidence

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In spite of the fact that efficient contraception is available in many countries, induced abortion is still a quite prevalent means of birth control, especially in certain subpopulations of women (young, socially deprived, etc). Judging by the published statistics, induced abortion rates vary dramatically between countries, with the lowest level being in West Germany (5.7 per 1000 women aged 15-44¹) and the highest in the Russian Federation of the USSR (123.6 in the mid-80s²).

Ever since its legalisation in 1955, induced abortion has been the primary means to reduce fertility in the USSR, resulting in 7 116 000 terminations in this country in 1986 (compared with only about 5 611 000 livebirths²), or 101.2 per 1000 women of reproductive age.² The real prevalence of induced abortion in the USSR is even higher than reflected by official statistics, since there is substantial underreporting in many areas, especially for the youngest and primigravid women.³ Results of a few surveys suggest that on average a sexually active woman has 2-4 induced abortions by the end of her reproductive period, and roughly 10-15% of the women have their first pregnancy interrupted.³ Induced abortion rates are highly differentiated between national, regional, and social subgroups of the population. Thus the range of variation between the national republics in registered induced abortion rates in 1985 was fourfold, ie, 30.8% in Azerbaidjan versus 123.6% in the Russian Federation.²

Sociodemographic and public health implications of multiple induced abortion in the USSR are well known: fertility reduction due to secondary postabortive sterility/subfecundity, high prevalence of chronic gynaecological conditions in young and middle aged women, obstetric complications, and high infant mortality.³⁻⁵ But up to now, clinical (and a few epidemiological) investigations have been focused on immediate and short term complications of induced abortion and its influence on subsequent reproductive function,⁵ while the long term cumulative effect of pregnancy termination has hardly been assessed. The issue of possible oncological implications of induced abortion discussed in this paper has traditionally been "no man's land" in a highly specialised medical science, as it has been missing from the curriculum of both oncologists and gynaecologists. Epidemiologically, induced abortion has also been neglected as a specific risk factor involved in causation of sex hormone

related cancers in women. To my knowledge, no study in this area has examined the potential effect of induced abortion in relation to length of gestation, termination procedure used, presence of immediate complications, etc.

This lack of attention is not easy to understand, since involvement of induced abortion in some stage of carcinogenesis in hormone dependent organs is biologically highly plausible. Some clinical and laboratory studies have shown that sudden interruption of the endocrine, immunological, neurological and other processes which adjust the organism to coexistence with the fetus cause a strong and long lasting impact, described by some investigators as a "hormonal blow".⁴ In cases of repeated induced abortion, such changes may accumulate, gradually producing chronic hormonal changes (such as progesterone deficiency) and/or immune disorders, to which psychological depression caused by this dramatic life event may also contribute.^{4,5} These shifts may lead to disturbance of mechanisms of cell differentiation and proliferation, weakening of immunity, and other systemic changes involved in malignant transformation.^{4,6-8} Therefore considering induced abortion in epidemiological analysis as just another short term pregnancy rather than a specific biological event may be misleading.

Breast cancer

Among hundreds of epidemiological studies of female breast cancer conducted all over the world, abortion is mentioned in no more than 20 papers. In many cases the authors do not even distinguish between spontaneous abortions, or miscarriages, and induced abortions—obviously quite different events, both biologically and socially. The lack of interest in induced abortion among Western epidemiologists probably reflects the relatively small perceived social significance of this factor in societies with developed contraceptive culture. Besides, in many Western countries induced abortion was illegal until recently, and female cohorts that have reached their breast cancer age had spent their reproductive years without opportunity of legal pregnancy termination. Hence European and North American epidemiologists did not have much chance to study induced abortion in terms of inherent cancer risk. In some studies where the authors intended to study induced abortion among other reproductive factors in breast cancer, the

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Accepted for publication
June 1990

numbers of respondents reporting such abortions were so small that the outcome statistical measures made no statistical sense. (In a case-control study by Brinton *et al.*,⁹ only 1.17% of cases and 1.20% of controls had ever had induced abortion.)

Due to limited number and low statistical power of the various studies that have been done the aetiological role of induced abortion and its relationships with other reproductive variables (particularly in terms of their relative timing) are dubious. Most of the studies considered termination of the first pregnancy as a risk factor for premenopausal breast cancer. The first of these, conducted by Pike *et al* in Los Angeles and published in 1981,¹⁰ had a strong impact on the epidemiological community. Comparison of reproductive histories of 163 women aged less than 33 years at diagnosis of breast cancer with two groups of age matched controls (neighbours and friends of presumably similar social status) showed that cases had significantly higher prevalence of both first trimester induced abortion and spontaneous abortion before their first full term pregnancy. The level of relative risk (RR) of 2.4, $p < 0.005$, did not decrease after adjustment for other reproductive variables, but was lower for women who subsequently had livebirths (1.8). Remarkably, abortions after 3 months of gestation or occurring after the first full term pregnancy did not affect the risk of early breast cancer.

Interpreting their results, Pike *et al* refer to the data from the international case-control study by MacMahon *et al.*,¹¹ showing that a terminated first pregnancy produced an increased rather than decreased breast cancer risk. The underlying hypothesis was that the long lasting protective effect of the first full term pregnancy was due to combination of cell differentiation and altered hormone profile after the first birth (the latter lasting for decades). As proliferation of the breast tissue occurs mainly in the early first pregnancy it is plausible that induced or spontaneous abortion after the first trimester of the first pregnancy has no sizeable effect on the risk.^{6 10}

After the study by Pike *et al* there have been at least four attempts to reproduce their results.^{9 12–14} In the retrospective cohort study by Hadjmichael *et al.*,¹² breast cancer risk was assessed among 33 115 women who had given their first birth between 1946 and 1965 in Connecticut. Reproductive histories of these women were obtained from their obstetric records, and breast cancer incidence in the cohort was followed up to the year 1980 through the Connecticut cancer registry. It was found that spontaneous abortion before the first full term pregnancy was associated with a 3.5-fold increase in breast cancer risk in comparison with women without history of spontaneous abortion, irrespective of the number of such abortions and other known breast cancer risk factors. Risk increased with time elapsed since the date of spontaneous abortion, so that over a 20 year period the overall breast cancer risk increased more rapidly in women who had had a spontaneous abortion. Unfortunately, there were no data on induced abortion before the first full term pregnancy in the obstetric records (since

they were illegal at the time), and interviews were not performed.

Interpreting these results, the authors addressed the experimental data of Russo and Russo,⁷ who analysed the influence of pregnancy in rats (full term, full term with subsequent lactation, and terminated) on the development of benign and malignant lesions in the mammary gland. They showed a protective effect of full term pregnancy, with and without lactation, against neoplastic changes in mammary gland via complete differentiation of mammary tissues. Hormonal changes of pregnancy affecting growth and differentiation of mammary cells (increases in oestrogens, progesterone and prolactin levels) were also shown to be protective. Pregnancy termination abruptly halts these processes, which results in underdevelopment of the mammary gland, making it more susceptible to malignant change. The animals with interrupted pregnancies had as high an incidence of tumours as virgin rats treated with a carcinogen. This experimental evidence may also be true for humans.^{8 12}

In the case-control study by Brinton *et al.*⁹ (1362 newly diagnosed breast cancer patients and 1250 healthy controls selected through the Breast Cancer Detection Demonstration Project in various parts of the USA) induced abortion emerged as a risk factor only for nulliparous women. Relative risk in these, as opposed to nullipara without induced abortion, was high enough to be close to statistical significance (5.5, with 95% confidence limits (CL) 0.8–36.8), although it was based on very small numbers. Another American study¹³ and one British case-control study¹⁴ failed to identify any risk associated with abortion before the first full term pregnancy, but in both studies the results were based on small numbers due to low prevalence of first pregnancy termination.

One earlier American investigation¹⁵ and three recent European studies^{16–18} have also given negative answers. A case-control study in the cities of Northern Italy¹⁶ (1108 newly diagnosed breast cancer patients and 1281 hospital non-cancer controls) produced non-significant relative risk measures: 1.18 for one induced abortion and 0.72 for two or more. But in women with one or more termination before the first full term pregnancy relative risk increased to 1.42 and was of borderline statistical significance (95% confidence interval 0.91–2.20). In the large screening programme based cohort study in Norway, women with induced and spontaneous abortions had a slightly decreased breast cancer risk, although non-significant and not showing a dose-response gradient.¹⁷ A cohort study of 49 000 women with a history of first trimester induced abortion in Sweden¹⁸ followed up in the cancer registry produced a relative risk estimate of 0.8 (95% CI 0.58–0.99).

However, in a number of studies from all over the world (in the USA, Canada, France, Denmark, Japan, and Israel) abortions, either multiple or occurring before the first full term pregnancy, have been shown to be significantly associated with increased breast cancer risk.^{19–28} In most cases, this evidence was related to induced abortion, though in a few studies it was

related to any pregnancy interruption. Relative risk values for this risk factor (in women with history of abortion(s) compared to those without, adjusted for other significant variables) were within the range of 1.5–4.0, ie, similar to most other reproductive characteristics.

A recent population based case-control study in Denmark,²⁶ including almost all the new breast cancer cases in the country for one year, has shown that induced abortion in the first and second trimesters of the first pregnancy was significantly associated with breast cancer risk (RR 1.43 with 95% CI 1.10–1.84). This relative risk value closely approximated that for nulligravid women (1.47; 1.14–1.90). Women with two or more induced abortions before their first full term pregnancy had a breast cancer risk of 1.73 (0.76–3.91) relative to those without induced abortions, all relative risk values adjusted for age, residence, and age at first birth. Here too, induced abortion after the first full term pregnancy did not significantly influence breast cancer risk (RR 1.35; 0.71–2.56).

The latest investigation specially addressing the issue of abortion and breast cancer was a population based record linkage study in upstate New York.²⁷ It was based on cancer registration data and fetal death reports, the latter containing data on all known spontaneous and induced abortions of any gestational length. History of fetal death was compared in 1451 breast cancer cases under the age of 40 years diagnosed during 1976–80, and 1451 population controls matching the cases by year of birth and residence. Matched pair analysis showed that termination of early pregnancy (mean length of gestation 9.6 weeks for case series and 11.5 weeks for controls) was significantly more frequent in breast cancer cases. Relative risk for induced abortion was 1.9 (95% CI 1.2–3.0) and for spontaneous abortion 1.5, but non-significant (0.7–3.7). Relative risk was the highest in women with a history of multiple terminations with no intervening livebirths (4.0; 1.5–13.6). On the whole, the number of interrupted pregnancies was 70% higher among cases, irrespective of the outcome of previous pregnancies.

In Canada, the 30 year follow up of a cohort of registered nurses²⁸ has shown that women with induced abortions had a significantly higher incidence of benign breast disease as compared to women with similar reproductive histories but without induced abortions.

In the Soviet Union where the potential public health impact of induced abortion might be much stronger than in the West, there have also been very few epidemiological studies directly assessing induced abortion as a cancer risk factor. Among other reproductive factors, it was evaluated in a case-control study in the North Caucasus.²⁹ Relative risk of breast cancer in women with three or more induced abortions was shown to be 3.4 times higher, and in those with one or two induced abortions twice as high as in women with no such history. Women who interrupted their first pregnancy when they were younger than 25 had a 1.8 times higher risk of breast cancer than those who had their first induced abortion later in life. Since the association between induced abortion and breast

cancer risk could be confounded by parity, these characteristics were analysed together and also stratified for two histological types of breast cancer (differentiated and undifferentiated). These stratified data have shown that in all subgroups by parity (0.1–1.3+), relative risk increased with number of induced abortions (1–2.3+), and for any given number of induced abortions the risk was lower for women with more livebirths. The highest risk of both breast cancer types was shown for nulliparous women with three or more induced abortions. The protective effect of higher parity was more clear for women with more induced abortions and differentiated tumours. This study therefore suggested an independent, and obviously inverse, aetiological impact of parity and induced abortion on breast cancer.

In another case-control study in Moscow with hospital controls similar to cases in terms of age, menopausal status, education and residence³⁰ no overall trend of breast cancer risk in relation to number of induced abortions was shown. The risk was slightly increased only in women with induced abortion before the first full term pregnancy. But this study also failed to show any role of other known reproductive characteristics involved with breast cancer (parity, lactation) and revealed only the age related aspect of reproductive activity as aetiological important. It may be argued that the Moscow population as a whole is unfavourable for epidemiological examination of reproductive risk factors because of the homogeneity of childbearing patterns of Muscovites with predominantly low fertility, the use of induced abortion as the means of birth control, and short lactational experience. Methodologically speaking, it is difficult to reveal aetiological significance in the case of a universally prevalent exposure.

Cervical cancer

Several studies have suggested a positive association between induced abortion and cancer of the cervix.^{23 31–38} Thus a case-control study in Paris and seven other French cities²³ has shown an almost fivefold increase in relative risk for women reporting two or more terminations (after adjustment for sexual and other significant variables). In the case-control study in Chile, the country with endemic cervical cancer rates, women with both induced and spontaneous abortion had significantly increased risk, although for spontaneous abortion it was somewhat higher (1.94 *v* 1.38).³²

Descriptive epidemiological studies in the USSR^{39–43} have suggested that regional variance in cervical cancer incidence is related more to induced abortion than to fertility rates. Thus the majority of cervical cancers in Armenia have been registered in three major cities—Yerevan, Leninokan and Kirovokan—where induced abortion rates have been high. In other towns and regions of this republic, with similar reproductive (and presumably sexual) population characteristics but half the induced abortion rate, the incidence of cervical cancer has been three times lower. The correlation coefficient between induced abortion rate and cervical cancer incidence in Armenia was 0.67.³⁹

Probably for the same reason, in the Central Asian Soviet republics, which have multinational populations, cervical cancer incidence in migrants, mostly Russians, is much higher than in indigenous women. For example, in Kirgizia, cervical cancer incidence in Russian women is five times higher than in Kirgiz women, while the accumulated numbers of induced abortions by the end of reproductive age is 3.3 for Russians *v* 1.8 for Kirgiz women.⁴⁰ This suggests that higher and earlier fertility in Kirgiz women (their expected number of children is about five *v* about two in Russians²) does not affect their cervical cancer risk.

The same relationship is more obvious for the USSR overall. A correlation study based on official abortion statistics and regional cancer incidence data for the period 1959–85⁴¹ showed a significant contribution of induced abortion to the variance of cervical cancer (and to a lesser extent also breast cancer) rates between areas of the country. The available statistical indicators of induced abortion prevalence (rate per 1000 women aged 15–49; induced abortion:livebirth ratio; proportions of registered out of hospital terminations and induced abortions in primigravidas in the total number of induced abortions have proved to be strong and consistent determinants of variation in the incidence of both female cancers (see table). This influence of induced abortion rates on regional distribution of cervical cancer and breast cancer (with adjustments made in correlation and regression analysis for the time lag between reproductive events and diagnosis) was independent of other reproductive characteristics studied (early marriage rates as a surrogate measure for early onset of sexual activity; age at first birth; parity; lactation).⁴¹

Suggested mechanisms of induced abortion influence on cervical carcinogenesis may be multiple. The first mode of action may be via general endocrine stress in the reproductive system resulting from termination of pregnancy related processes. Another is through mechanical trauma and possible infection associated with dilatation and curettage or incomplete evacuation of the embryo and placenta. Chronic inflammatory lesions may arise in cervical tissue on the site of this trauma (erosions, endocervicitis, leucoplakia), as well as cell abnormalities (dysplasias). In course of time, the latter may undergo malignant transformation and/or facilitate the action of exogenous carcinogenic agents.^{4 34 42 43} Such a pathogenic chain is in good agreement with the concept of three stage cervical

carcinogenesis: from dysplasia (mild, moderate, and severe) to carcinoma *in situ* and invasive carcinoma.^{34 42} It has also been shown that dysplasias and intraepithelial neoplasms of the cervix are more prevalent in women with the history of induced abortion.^{32 35 42}

Ovarian cancer

The possible influence of abortion on ovarian cancer development is obscure and has hardly ever been specifically examined. Most of the studies of ovarian tumours have been directed towards two protective reproductive factors: pregnancy experience *per se*, and hormonal contraception as an imitator of pregnancy experience, both acting by decreasing the total period of ovarian activity.^{44–46} A few studies have suggested no effect^{45 46} or a weak and non-significant protective effect^{47 48} of both induced and spontaneous abortion. A recent case-control study in Japan has shown a significant protective effect of induced abortion, with their numbers not specified, on ovarian cancer risk (RR 0.6, 95% CI 0.3–0.9) when a few other reproductive variables were controlled for.⁴⁹ No mechanism of this protective action is suggested by the authors other than that short term pregnancies are added to the total pregnancy experience.

Endometrial cancer

No special evidence is available on the role of induced abortion in the causation of endometrial cancer, although here an effect is biologically plausible since the inner lining of the uterus is the site of dilatation and curettage or vacuum aspiration procedures. As with ovarian tumours, several authors have argued that the more pregnancies a woman had had, regardless of whether they proceed to term or not, the lower her risk of endometrial cancer,⁵⁰ although the protection conferred by an incomplete pregnancy is much smaller than that of a full term one: as estimated by Henderson *et al*⁵¹ 5–6 pregnancies terminated by induced or spontaneous abortion roughly equal one pregnancy resulting in a livebirth. In a Norwegian cohort study by Kvale *et al*,⁵² there was no definitive trend in endometrial cancer risk according to the number of induced or spontaneous abortions. Among parous women, the odds ratio for those with three or more abortions, as compared to abortion free subjects, was 1.03 (95% CI 0.58–1.82) in logistic regression analysis with adjustment for parity, age at first birth, and some demographic variables.

Correlation between statistical indicators of abortion and age adjusted incidence rates of breast cancer and cervical cancer for women of 70 areas of Russia

Abortion indicators and outcome variables	Time lag (years)	Parametric tests			Non-parametric rank criteria	
		<i>r</i>	<i>r_p</i>	ζ	Spearman ρ	Kendall τ
Abortion rate, %	10	0.45	0.23	0.25	NS	NS
Breast cancer	10	0.77	0.63	0.76	0.77	0.57
Cervical cancer						
% of out of hospital abortions	0	0.80	0.48	0.36	NS	NS
Breast cancer	0	0.53	NS	0.34	NS	NS
Cervical cancer						
% of abortion in primigravid women	0	0.65	0.22	0.79	0.45	0.29
Breast cancer	0	0.58	0.33	0.29	NS	NS
Cervical cancer						

Cited from Remennick⁴¹

Coefficients used: *r* = linear (Pearson's); *r_p* = partial; ζ = correlation ratio

Abortion/livebirth indicator is not shown since its meaning is close to that of abortion rate, and so are the coefficients

No studies could be found relating abortion to the risk of any non-reproductive cancer.

Conclusion

Two competing approaches can be seen in the studies assessing induced abortion as a potential cancer risk factor and as a biological event generally. The first attitude tends to stress the pregnancy per se, short or full term, with all its protective changes (differentiation of breast tissues, intermission in ovarian activity, etc). Therefore, an interrupted pregnancy is considered as a legitimate supplement to the total pregnancy experience, and calculations such as "5.6 terminated pregnancies = 1.0 full term pregnancy"⁵¹ are the logical extension of this viewpoint. Hence terminated pregnancies are considered as protective, or at least neutral, reproductive events.^{14-17 44-52}

The alternative approach is focused not so much on pregnancy experience but rather on the fact of its sharp termination with concomitant hormonal and immunological stress, incomplete differentiation and growth of breast tissues, etc. The above mentioned calculation would be irrelevant within this approach, and its proponents see abortion as a risk factor.^{7 8 10 12 23 25-27 29 35 37 41-43} An initial attitude of researchers towards abortion usually determines the way they interpret results, since outcome risk measures are often of moderate value and/or borderline statistical significance. There are rational arguments for both approaches, but the second seems more plausible biologically and is also backed up by certain clinical and experimental data.

The role of induced abortion in female cancers obviously needs further scrutiny, preferably in analytical studies specially addressing this issue and in populations with high induced abortion rates (so far all but a few studies have been conducted in the countries with low/moderate induced abortion rates). One of the questions to be clarified is the suggested cross over effect in the action of pregnancy related risk factors for breast cancer.^{8 15 21 53} Is it true that any pregnancy, including one terminated by abortion, confers protection in the long run (ie, for post-menopausal breast cancer) but increases the risk during reproductive years? Is the effect of pregnancy termination separate and opposite to the effect of pregnancy per se? How does induced abortion add to a woman's reproductive cancer risk profile when performed at various ages, before, after, or in between live births?

So far, two categories of women have been shown to experience increased breast cancer risk due to induced abortion: those with terminated first pregnancy,^{8 10-12 25 29 30 41} and nulliparous women.^{8 9 27 29} But both findings have been challenged in other studies.^{13 14 16 17} Another aspect of the problem is possible accumulation of risk with multiple terminations, highly prevalent in the USSR and some other countries. Yet another question to be answered in future studies is whether the gestational age and type of termination technique (dilatation and curettage, vacuum aspiration, prostaglandins, and other abortifacients) influence subsequent cancer risk,

and in what way. And, finally, what are the intermediate pathogenic stages between induced abortion and the development of cancer of the cervix uteri (and probably also of the corpus uteri)?

As in most other cancer aetiology puzzles, both epidemiology and other sister disciplines (clinical and experimental oncology, gynaecology, social medicines, etc) can contribute to an improvement of our understanding of abortion as a factor in carcinogenesis.

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