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TITLE: Risk of Breast Cancer Among Young Women: Relationship to Induced Abortion

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ABSTRACT: Background: Certain events of reproductive life, especially completed pregnancies, have been found to influence a woman's risk of breast cancer. Prior studies of the relationship between breast cancer and a history of incomplete pregnancies have provided inconsistent results. Most of these studies included women beyond the early part of their reproductive years at the time induced abortion became legal in the United States. Purpose: We conducted a case-control study of breast cancer in young women born recently enough so that some or most of their reproductive years were after the legalization of induced abortion to determine if certain aspects of a woman's experience with abortion might be associated with risk of breast cancer. Methods: Female residents of three counties in western Washington State, who were diagnosed with breast cancer (n = 845) from January 1983 through April 1990, and who were born after 1944, were interviewed in detail about their reproductive histories, including the occurrence of induced abortion. Case patients were obtained through our population-based tumor registry (part of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute). Similar information was obtained from 961 control women identified through random digit dialing within these same counties. Logistic regression analysis was used to estimate odds ratios and confidence intervals (CIs). Results: Among women who had been pregnant at least once, the risk of breast cancer in those who had experienced an induced abortion was 50% higher than among other women (95% CI = 1.2-1.9). While this increased risk did not vary by the number of induced abortions or by the history of a completed pregnancy, it did vary according to the age at which the abortion occurred and the duration of that pregnancy. Highest risks were observed when the abortion was done at ages younger than 18 years -- particularly if it took place after 8 weeks' gestation -- or at 30 years of age or older. No increased risk of breast cancer was associated with a spontaneous abortion (RR = 0.9; 95% CI = 0.7-1.2). Conclusion: Our data support the hypothesis that an induced abortion can adversely influence a woman's subsequent risk of breast cancer. However, the

results across all epidemiologic studies of this premise are inconsistent -- both overall and within specific subgroups. The risk of breast cancer should be reexamined in future studies of women who have had legal abortion available to them throughout the majority of their reproductive years, with particular attention to the potential influence of induced abortion early in life.

TEXT:

In 1973, the Supreme Court legalized induced abortion in the United States. Since that time, this procedure has been used by many women to terminate unwanted pregnancies. The Alan Guttmacher Institute estimates that as of 1990, one in four U.S. women younger than 45 years of age had had at least one induced abortion (Henshaw SK: personal communication). Since the timing and number of completed pregnancies are known to affect a woman's risk of breast cancer [n1], it is possible that a history of terminated pregnancies may have an effect as well.

In 1981, Pike et al. [n2] reported a 2.4-fold increase in the risk of breast cancer among young women (aged younger than 33 years) that was associated with a first-trimester induced abortion prior to a full-term pregnancy. While additional studies have examined the general question of induced abortion as a risk factor for breast cancer [n3-n10], they primarily included women who, by the early 1970s, already were beyond the early part of their reproductive lives. Thus, the studies have been limited, to some extent, in their ability to evaluate the impact of an abortion at a relatively young age or prior to a first pregnancy.

We conducted a case-control study of breast cancer in young women born recently enough to have had some or most of their reproductive years after the legalization of induced abortion to determine if there were certain aspects of a woman's experience with abortion that might be associated with her risk of breast cancer.

Patients and Methods

All white women diagnosed with a first invasive or in situ breast cancer between January 1, 1983, and April 30, 1990, who were residents of King, Pierce, or Snohomish County in Washington State and who were born after 1944, were eligible for the study. We restricted our study to white women, since approximately 85% of this population is white and no minority group makes up more than 5% of the population. These women were identified through the Cancer Surveillance System, a population-based tumor registry that serves 13 counties in western Washington State and is part of the Surveillance, Epidemiology, and End Results (SEER) Program n1 of the National Cancer Institute (NCI). Of the 1011 eligible cases, 845 (83.6%) were successfully interviewed. Reasons for not obtaining an interview for case patients included the following: deceased (n = 58; 5.7%), patient refusal (n = 71; 7.0%), and physician refusal to give permission (n = 37; 3.7%). Ninety-eight of the case patients interviewed had been diagnosed as having an in situ lesion.

n1 Editor's note: SEER is a set of geographically defined, population-based central tumor registries in the United States, operated by local nonprofit organizations under contract to the NCI. Each registry annually submits its cases to the NCI on a computer tape. These computer tapes are then edited by the NCI and made available for analysis.

Controls were recruited by random digit dialing, using the method described by Waksberg [n11]. To minimize geographic clustering of controls that can occur using the Waksberg-Mitofsky method of random digit dialing, we used a clustering factor of two residences per sampling unit (denoted "k" by Waksberg). Use of a "k" of 2 resulted in no more than two controls per sampling unit, although the majority of sampling units yielded either one or no controls. All telephone numbers were called at least nine times at different times of the week during a 2-to 6-week period before they were abandoned. Telephone numbers that resulted in refusals to answer the screening questions were called again by a different interviewer 4-6 months later. One half of the initial refusers were successfully screened on the second attempt. One-step recruitment was used, with a stratified sampling design that recruited controls into age strata evenly throughout the control ascertainment period [n12,n13]. The King County controls were shared by another study, therefore age stratification requirements were determined by the study needing the largest number of controls. Eligible women who agreed to receive a letter about the study were contacted within 3 weeks of the initial random digit dialing contact by an interviewer to schedule a personal interview. We were unable to determine residential status after nine or more attempts for 4% of the telephone numbers dialed (3%: "no answer," 0.2%: "slow busy" [tone repeated 60 times per minute], and 0.5%: "fast busy" [tone repeated 120 times per minute]). In the past, we found the majority of these numbers to be non-residential. We were able to obtain a household census for 97% of the known private residences. Of the 1239 respondents who met the study's residence and age requirements, 961 (78%) were successfully interviewed for a final overall response rate of 75.5%.

All but 1.8% of the interviews were conducted in person. To aid the women's recall, trained interviewers used a calendar on which major life events were identified. Only events that took place before each woman's reference date (month and year of diagnosis for the case patients and a comparable date for controls) were recorded. Demographic, lifestyle, and medical-history data were obtained, as well as data on family history of breast and other cancers. We also obtained a detailed history of birth-control methods used by each woman. A complete menstrual and pregnancy history was obtained for all women. For each induced or spontaneous abortion reported, questions were asked regarding the gestational age (number of weeks or 1-8, 9-12, 13-16, or > 16 weeks) and method of birth control (if any) at the time of conception. In addition, the type of procedure was ascertained for each induced abortion.

Logistic regression analysis using EGRET (Statistics and Epidemiology Research Corp., Seattle, Wash.) statistical software was used to estimate odds ratios (ORs) and confidence intervals (CIs) associated with induced abortion. The primary focus of the analysis was on the difference in the subsequent risk of breast cancer between pregnant women who did and did not choose to terminate that pregnancy but who, based on their demographic characteristics and childbearing histories, were otherwise at similar risk. Thus, all analyses presented are adjusted for age (continuous), family history of breast cancer (none, mother or full sister, or grandmother, aunt, or half sister), religion (none/Jewish/other, Catholic/Mormon/Seventh-day Adventist, or other Christian), and age at first pregnancy (11-17, 18-19, 20-29, or 30-41 years). Adjustment for age at first birth was done in analyses that were restricted to parous women (women who ever had a live birth or stillbirth). Further adjustment for the following variables did not change the ORs: oral contraceptive use, other contraceptive methods, obesity, number of births, reference year, county of residence, alcohol use, cigarette smoking history, age at menarche, income, education, and marital status. Analyses relating to gestational length were restricted to the categories 1-8, 9-12, and 13 or more weeks, since the women who did not know the exact number of weeks of gestation were asked to report which of the above gestational categories best represented their experience. Analyses for spontaneous abortion were adjusted for age, marital status (never married, currently or formerly married, or living as married), family history of breast cancer, age at first live birth, and body mass index (quartiles). The term relative risk (RR) is used hereafter instead of odds ratio, since the two have similar values in case-control studies of other than very common diseases.

Results

On the average, controls in our study were somewhat younger than the breast cancer case patients (Table 1). Adjusting for age, an increased risk of breast cancer was associated with early age at menarche, nulliparity, and having a first- or second-degree relative who had breast cancer. In contrast, parous case patients and controls were similar with respect to age at first birth and number of children. Women in the highest quartile of body mass index had a 20% reduction in breast cancer risk. The proportion of control participants with a history of induced abortion decreased with increasing age and increasing parity and differed by religious affiliation (Table 2). However, that proportion varied little by other characteristics.

Table 1. Characteristics of breast cancer case patients and controls

[SEE ORIGINAL SOURCE]

Table 2. Characteristics of controls by history of induced abortion and by history of spontaneous abortion

[SEE ORIGINAL SOURCE]

Among women who had been pregnant at least once, a history of induced abortion was associated with an increased risk of breast cancer (RR = 1.5; 95% CI = 1.2-1.9) (Table 3). The RR was also 1.5 (95% CI = 1.2-2.0) in women who had given birth at least once, adjusting for age at first full-term pregnancy. When we confined this analysis to parous women whose only pregnancies were live births and/or induced abortions, the RR was 1.6 (95% CI = 1.2-2.3). The magnitude of the association did not vary substantially by whether the induced abortion preceded or followed a first birth or by the interval from first abortion to cancer diagnosis. The magnitude of the increase in risk of breast cancer was similar between women who had one or more than one induced abortion. The RR associated with having an induced abortion was 1.8 (95% CI = 1.2-2.9) in women younger than 35 years at diagnosis and/or reference date; it was 1.4 (95% CI = 1.0-1.9) in 35- to 44-year-old women. While pregnancies terminated by an induced abortion at 9-12 weeks' gestation were associated with a somewhat higher risk than those terminated earlier, that trend was not continued in the small number of abortions that took place beyond 12 weeks. The elevation in risk associated with induced abortion was greater in women who underwent their first induced abortion either before 18 years of age (RR = 2.5; 95% CI = 1.1-5.7) or at age 30 years and older (RR = 2.1; 95% CI = 1.2-3.5) (Table 3). The risk associated with abortion did not vary by early or late stage of disease at diagnosis. Among women who had an induced abortion as a teenager, there was no variation in risk by age at menarche (data not shown).

Table 3. Risk of in situ and invasive breast cancer in gravid women associated with prior induced abortion

[SEE ORIGINAL SOURCE]

We examined the combined influence of age at first induced abortion and the gestational length at the time the abortion occurred. Fifteen case patients, but only five controls, had terminated a pregnancy when younger than 18 years of age that had lasted more than 8 weeks (adjusted RR = 9.0; 95% CI = 2.0-41.2) (Table 4). Abortions at ages younger than 18 years that occurred earlier in gestation were associated with a far smaller increase in risk (RR = 1.3; 95% CI = 0.3-7.0) (Table 4). There was little variation in risk associated with the gestational timing of an abortion during a given pregnancy if the first abortion took place at 18 years of age or older. We obtained similar results when we analyzed the timing and duration of a woman's last induced abortion (for most women, the first abortion was also the last abortion).

Table 4. History of induced abortion in women with in situ or invasive breast cancer and controls, by age at first induced abortion or birth and by length of that pregnancy

[SEE ORIGINAL SOURCE]

In women with no family history of breast cancer, the overall size of the increased risk associated with a history of induced abortion was 1.4 (95% CI = 1.0-1.9) and varied little by the age at which the first induced abortion occurred (data not shown). In women with a positive family history (defined as a sister, mother, aunt, or grandmother with breast cancer), the overall risk was 1.8 (95% CI = 1.1-1.3) and was particularly strong for a first abortion that occurred prior to age 18 years (12 case patients and zero controls; RR = infin, ; lower 95% CI of RR = 1.8) and at age 30 years or older (14 case patients and three controls; RR = 3.7; 95% CI = 1.0-13.4).

Among parous women who never nursed a child or had nursed less than 1 month, there were similar risks associated with a history of induced abortion whether or not it preceded their first delivery (Table 5). There was a suggestion that, among women who later nursed a child, the association with induced abortion was stronger the longer the interval from the time of the first abortion until the initiation of lactation. The association of induced abortion with breast cancer was also present if the first abortion did not occur until after a woman already had nursed a child (RR = 1.9; 95% CI = 1.1-3.1) (Table 5).

Table 5. Risk of in situ and invasive breast cancer in relation to history of lactation and induced abortion among parous women

[SEE ORIGINAL SOURCE]

Since some women may view induced abortion as an alternative to contraception, and may not consider having a full-term pregnancy at all, we performed one analysis comparing women who never had a pregnancy with women whose only pregnancy ended in an induced abortion. Sixty-three case patients and 53 controls in this subgroup had undergone an induced abortion, corresponding to an RR of 1.4 (95% CI = 0.9-2.2).

We also evaluated the relationship of spontaneous abortion to risk of breast cancer. Women who had a history of spontaneous abortion were older and were more likely to be currently married, to be living as married, or to have been married in the past than women who had not had a spontaneous abortion (Table 2). They were more likely to have had a first birth at a young age, to have had three or more live births, and to be heavier.

Among women who were parous (more than 90% of the case patients and controls with a history of spontaneous abortion), there was no overall increase in risk for breast cancer (Table 6); however, there was some indication that women whose first spontaneous abortion occurred at age 18 or 19 years might be at increased risk. In addition, among women who had a spontaneous abortion, those with breast cancer were more likely to have had the first spontaneous abortion

occur at 9-12 weeks' gestation than at 1-8 weeks' gestation. Among women who had never delivered a child or had any other pregnancy outcome, there was no increase in breast cancer risk related to a history of spontaneous abortion (RR = 1.1; 95% CI = 0.4-2.6), based on 14 case patients and 12 controls who had a spontaneous abortion.

Table 6. Risk of in situ and invasive breast cancer in parous women associated with prior spontaneous abortion

[SEE ORIGINAL SOURCE]

None of the foregoing results were materially influenced when we excluded from the analyses the 98 women with an in situ lesion only.

Discussion

We were able to interview only 83.6% of the breast cancer case patients and 78% of the controls. If those not interviewed differ from the interviewed women regarding history of induced abortion, our results would be biased. Olsson et al. [n14] found that the breast tumors of women who had a spontaneous or induced abortion at a young age had a higher rate of cell proliferation and a higher frequency of aneuploid tumors compared with the tumors of other young women with breast cancer. These same investigators also found that early abortion was related to INT2 amplification [n15]. Since these tumor characteristics are related to a poor prognosis [n16], it could be that those women with breast cancer whom we were unable to interview because of serious illness or death may have been more likely to have had an induced abortion than the women we did interview. If this bias were present, we would have underestimated the risk of breast cancer that is associated with induced abortion.

A second concern is the accuracy of reporting of induced abortion by case patients and controls. Our interviews took place from the mid 1980s through the early 1990s, a time when induced abortion was common and well accepted among U.S. women. We designed the study to focus largely on legal induced abortion by restricting our study subjects to women born after 1944, i.e., by including women in whom most or all of their reproductive years occurred after 1970 (the year in which induced abortion was legalized in Washington State). Of the 411 induced abortions reported by study participants, 371 (90.3%) took place in 1970 or later. Thirty of the 35 abortions (85.7%) reported as having occurred in women younger than 18 years of age were during the era of legalized abortion.

It is possible that a woman diagnosed with a life-threatening disease such as breast cancer might report a history of induced abortion more completely than a healthy control woman contacted at random. Lindefors-Harris et al. [n17] evaluated this hypothesis by linking responses to interview questions on induced abortion from Swedish case patients and controls in a study of breast cancer to

national registry data on abortions occurring in 1966-1974. Nineteen (79.2%) of 24 case patients listed in the national registry as having had an induced abortion reported it during the interview, in contrast to 42 (71.2%) of 59 controls. Complicating the interpretation of this difference was the fact that no national registry record of an abortion could be located for seven other case patients, but only one other control, who claimed to have had an abortion during 1966-1974. Lindefors-Harris et al. compared ORs for an induced abortion-breast cancer association using interview data alone and then data from the national registry alone and concluded that a spurious 50% increase in risk could be obtained from interviews. However, we believe it is reasonable to assume that virtually no women who truly did not have an abortion would claim to have had one, and thus to assume those study participants whose reported abortion could not be documented (a) were incorrect when stating that the year of their abortion was within the period 1966-1974 or (b) had undergone the abortion outside of Sweden. If these assumptions are correct, it is possible to calculate ORs obtained from interview data alone with those obtained using a positive statement of an induced abortion in either interview or registry data as the standard. When we calculate this OR, the size of the spurious increase in risk that arises from reporting differences between case patients and controls is only 16%.

To further examine the possibility of differential reporting, we assessed the risk of invasive cervical cancer associated with a history of induced abortion among 214 case patients in western Washington State who were younger than 45 years of age and 321 controls obtained through random digit dialing (unpublished data from a population-based case-control study). After adjusting for age at reference date, age at first intercourse, number of lifetime sexual partners, income, and smoking history, the RR of cervical cancer in relation to an induced abortion was 1.0 (95% CI = 0.7-1.6). Unless a history of an induced abortion were truly negatively associated with the incidence of invasive cervical cancer, this result argues against there being differential reporting of prior induced abortions by cancer case patients and controls among reproductive-age women in western Washington State.

We were not able to validate the histories of induced abortion and had to rely solely on the respondents to provide information regarding the gestational length of incomplete pregnancies. However, we believe it is likely that the reporting of gestational length would be neither more nor less accurate for controls than for case patients. We were also unable to validate the histories of spontaneous abortion. We did ask at interview if the pregnancy that resulted in the spontaneous abortion was verified by a physician and/or a pregnancy test. Ninety percent of the case patients and 87% of the controls indicated the pregnancy had been so verified. Our results did not change when we restricted our analyses to verified spontaneous abortion.

The results of some epidemiologic studies [n2-n4], including this study, support the hypothesis that women who have undergone an induced abortion are at a

40%-90% increased risk of developing breast cancer later in life. However, other studies have found little evidence of such a relationship [n5-n9,n18]. This mixed pattern of results is present whether the studies ascertained abortion status on the basis of interview or through records that documented the procedure.

We addressed the possibility that an elevated risk of breast cancer might be associated with only some induced abortions, perhaps those that occurred at a certain time in life, in a certain relationship to other events of reproductive life, or after a minimum gestational length. In doing so, we paid particular attention to the hypothesis that reproductive events occurring at the time of development of the breast affect the proliferation and hormonal regulation of the breast decades later [n19]. This hypothesis is supported, in part, by studies on experimental animals [n20], indicating that chemically induced carcinogenesis is directly related to the rate of cell proliferation of the gland at the time of exposure to the carcinogen and that the rate of cell proliferation is highest in young nulliparous animals.

Russo et al. [n21] have studied the effect of pregnancy interruption in the young rat. In the 7,12-dimethylbenz[a]anthracene (DMBA) model system, the hormonal changes of pregnancy accelerated tumor development in rats that mated after administration of DMBA, whereas a single pregnancy prior to feeding the carcinogen to the rat was protective against tumor development. However, when the rat's pregnancy was interrupted (by hysterectomy at midpregnancy), the differentiation of the mammary gland was not completed and these animals had nearly the same tumor response to subsequent DMBA administration as did virgin animals. They hypothesized that the incomplete differentiation of mammary gland cells during the first trimester may increase the subsequent susceptibility of breast tissue to carcinogenic agents [n22].

The results of epidemiologic studies are in only partial accord with predictions based on these animal models. Our data suggest that abortions performed at a very early age are associated with an increased risk of breast cancer; women who underwent an induced abortion when younger than 18 years of age had a subsequent 2.5-fold increase in risk compared with women who have been pregnant and never had an induced abortion. While the only other study to examine the possible effect of early abortion (defined as occurring at younger than age 20 years and confined to nulliparous women) [n6] found no increase in risk, the authors did not further divide this category to consider abortions done very early in reproductive life. Nonetheless, even in our own results, the association with induced abortion was not restricted to procedures performed during the teenage years, since we observed a 2.1-fold increase in risk among women whose first abortion did not occur until age 30 years or older.

A possible explanation for our observation of a variation in risk of breast cancer associated with induced abortion according to age at first induced abortion could involve the change in the distribution of breast lobule types with age. Russo et al. [n23], using mammoplasty specimens from the breasts of women with various

reproductive histories, characterized four different lobular structures in the breast. Lobules type 1 are the most undifferentiated ones and are the site of origin of preneoplastic lesions that evolve to ductal carcinoma in situ, with progression to invasive carcinoma. Lobules types 2, 3, and 4 are less likely to be the site of tumor development. The proportion by age of type 1 structures follows a U-shaped curve, being relatively high in women younger than 19 years, lowest in women aged 24-28 years, and thereafter increasing in frequency with age.

There are considerably more epidemiologic data to evaluate the possible influence of an induced abortion prior to a first pregnancy on the incidence of breast cancer, and here, too, the results are not completely in accord with the results in experimental animals. In our study, there was no appreciable difference in risk with regard to whether the first induced abortion occurred in the absence of a subsequent term pregnancy or prior to or following a term pregnancy. In this regard (although not necessarily in terms of the overall relationship of induced abortion to breast cancer), our results were similar to those obtained by Adami et al. [n7], Yuan et al. [n9], Harris et al. [n18], and Parazzini et al. [n5]. Ewertz and Duffy [n4] and Brinton et al. [n10] observed a several-fold increase in breast cancer risk (based on a modest number of subjects) in nulliparous women who had undergone an induced abortion but no increase in risk in those whose abortion preceded or followed a subsequent term pregnancy. Finally, Pike et al. [n2] found a several-fold increased risk associated with abortion (induced or spontaneous) in nulliparous women, a 1.8-fold increase if the abortion preceded a term pregnancy, and no increase if the abortion was followed by a term pregnancy.

Some epidemiologic studies of breast cancer in young women [n1,n24,n25], as well as animal studies [n21,n22,n26], indicate that breast-feeding protects against the development of breast cancer. If pregnancy interruption leaves undifferentiated structures in the breast, we hypothesized that a full-term pregnancy followed by lactation relatively soon after an induced abortion may push those cells to full differentiation. Our results offer some support for this hypothesis (Table 5) in that induced abortion was not associated with an altered risk of breast cancer in women who nursed a child during the 5 years following the abortion. However, the relatively small number of women with this history argues for a cautious interpretation.

During the first trimester of pregnancy, the breast is characterized by high mitotic activity and proliferation; only in midpregnancy to late pregnancy does cellular differentiation predominate [n27]. Therefore, it is plausible that those pregnancies that are not interrupted until the end of the first trimester could result in the breast containing a high number of undifferentiated cells, relative to the breasts of women whose abortion was induced early in pregnancy (or who had no abortion at all). Conceivably, these morphologic differences could be related to differences in the subsequent incidence of breast cancer as well. Unfortunately, there is but limited information from epidemiologic studies on breast cancer risk in relation to when during pregnancy an induced abortion had been performed. Neither Ewertz

and Duffy [n4] nor Pike et al. [n2] observed any increased risk of breast cancer associated with a prior second-trimester abortion, but they did not address the issue of the impact of late first-trimester abortion. In the study of Howe et al. [n3], the authors reported that prior abortions in breast cancer case patients occurred on average at 9.6 weeks' gestation, as opposed to 11.5 weeks in controls. While the difference is in the opposite direction of that predicted, the very short duration of follow-up after the induced abortions in that study (1-10 years) severely limits its interpretation.

Prior studies of breast cancer in relation to spontaneous abortion have not yielded consistent results [n1]. We did not observe an increased risk of breast cancer among women who had a history of a spontaneous abortion. We can only speculate on why this result did not parallel that for induced abortion. We did observe that only 14.3% of women who had had an induced abortion nursed a child during the 5 years following the abortion compared with 46.3% of women with a spontaneous abortion. However, when we excluded from the analysis those case patients and controls who had experienced a spontaneous abortion and then nursed during the next 5 years, no excess risk of breast cancer associated with spontaneous abortion was seen (RR = 1.1; 95% CI = 0.8-1.5). Another possible explanation may be the relatively short gestational length of many pregnancies that end in spontaneous abortion. In their study of tissue from abortuses, Fantel and Shepard [n28] estimated that, on the average, the majority of the fetuses that had spontaneously aborted had spent approximately 24 days in utero following the cessation of fetal growth.

The data from the present study suggest that induced abortion in the last month of the first trimester is associated with nearly a doubling of subsequent breast cancer risk (Table 3). While the difference in risk associated with an abortion prior to and following 2 months of gestation was particularly great when the abortion occurred at a very young age (Table 4), the relatively small number of subjects in that subgroup and the lack of a corroborating study argue against a firm conclusion at this time. For the same reasons, the particularly large case-control differences regarding very young or older age at first induced abortion in women with a positive family history of breast cancer should be viewed only as hypotheses worthy of subsequent testing.

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