The Low Incidence of Cervical Cancer in Jewish Women: Has the Puzzle Finally Been Solved?

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Cervical carcinoma is one of the most common gynecologic malignant tumors worldwide and a leading cause of death from genital malignancies in women. One of the most important epidemiologic observations concerning this neoplasm is that the disease is practically non-existent in celibate populations. This was first noticed in the 19th century by Rigonni-Stern [1] of Verona, Italy, regarding Catholic nuns, who are sexually inactive. Gagnon of Quebec [2] subsequently confirmed this observation. He served as a gynecologist in a few Quebec nunneries for several years, and it occurred to him that he had never seen a case of cancer of the cervix in a nun. Among 13,000 deaths of nuns, 12 were recorded as due to corpus cancer. If the same ratio of cervix to corpus cancer exists among nuns as among the general population, there should have been 5 to 8 times as many cervical cancers. Instead there was none. These observations and the subsequent identification of risk factors led to the conclusion that cervical cancer is associated with coitus, and that it shares many characteristics with communicable diseases which follow a venereal mode of transmission. These findings led eventually to the identification towards the end of the 20th century of the human papillomavirus and its major etiologic role in this neoplasm [3–5].

A potentially similarly important observation was published by Braithwaite [6] in *The Lancet* in 1901. Referring to the experience with cancer of the cervix at the Leeds General Infirmary and at the London Hospital, he stated that it "was seldom or never met with amongst the numerous Jewesses" attending these institutions. Although the low incidence among Jewish women has been repeatedly confirmed since then, the reason for it has intrigued and eluded many investigators.

The purpose of the present review is to survey investigations concerning cervical cancer in Jewish women, with special emphasis on attempts made to elucidate the reason for the infrequency of this neoplasm among this population, including the most recent genetic study.

Since the report by Braithwaite [6], numerous publications have verified his observation. Hochman et al. [7] cite 14 individual studies published from 1902 to 1947, all indicating the low frequency of cervical carcinoma in Jewish women. Kennaway, in 1948 [8], published an extensive summary including reports from various cities in the United States and many countries in Europe, all pointing to the infrequency of cervical carcinoma in Jewish women. Many additional reports on the low occurrence of cancer of the cervix in Jewish women were published in the U.S. in the 1950s and 1960s [9,10]. The ratio between Jewish and non-Jewish patients with cancer of the cervix was variously calculated at between 1/9 and 1/5.

After the State of Israel was established in 1948, even more studies were published indicating the low occurrence of cervical cancer in Israeli Jewish women [7,11]. Hochman et al. [7] reviewed all the cervical carcinoma cases registered between 1933 and 1951 at the Hadassah University Hospital in Jerusalem. Since radical operations were not performed in the country at that time, and this was the only hospital that could administer radium therapy, they assumed that the 125 cases they located (only 67 of which were histologically confirmed) represent all the cases diagnosed in Jewish women. They were the first to consider ethnic differences within the Israeli Jewish population. Their study compared three ethnic groups: the Mizrahi (Oriental) – i.e., descendants of those born in Iraq, Syria, Persia, Yemen and North Africa; the Sephardic (Spanish) – descendants of those born in Spain, Portugal and some Mediterranean countries; and the Ashkenazi – descendants of those born in Eastern Europe. But they found no incidence difference between the Ashkenazi and non-Ashkenazi groups. Stewart et al. [12], in the early 1950s, conducted an extensive interview and incidence study of cervical cancer, comparing Israeli Jewish women with Jewish and non-Jewish white women in New York City. In Israel, the interviewers were located in three medical centers in the major cities and were notified of new patients by staff members of hospitals in and around these cities. In addition, cases were located from records of hospital discharges and death certificates. The Central Bureau of Statistics provided an estimate of the female population of Israel, classified by age and country of birth. The incidence rates of cervical cancer in Israeli Jewish women and Jewish women in New York City were virtually identical (4.8 and 4.1 respectively), and strikingly lower than the rate in non-Jewish white women (15.0). Similar to the findings of Hochman's study [7], the rates in the Ashkenazi and Sephardi-Oriental subgroups were also virtually identical (4.7 and 4.9 respectively). In 1960 the Israel Cancer Registry was established. This registry is notified by law of all new cancer patients and obtains its information from three sources: hospital records, pathologic reports, and death certificates. Steinitz and Costin [13] published the first population-based incidence rates of cervical cancer, again showing that they are markedly low in Israeli Jewish women. Between 1960 and 1967, only about 60 new cases were diagnosed annually throughout Israel, and

the incidence rate was about 5.8. Subsequently, when differences between ethnic groups were analyzed by continent of birth and not by allocation to Ashkenazi and Sephardi-Oriental subgroups, appreciable differences were noted. Modan et al. [14], and later Sharon et al. [15], reported that the incidence of cervical carcinoma among Jewish women born in North Africa was considerably higher than in those born in the other continents, mainly due to the high incidence in women born in Morocco. This observation was subsequently confirmed by Menczer and colleagues [16]. Their study included all cases of cervical cancer diagnosed in Israel during the 11 year period 1961–71. They found that the mean age-adjusted incidence rate in North African-born Jewish women was statistically significantly higher than in women born in Europe, Asia and Israel (8.3 vs. 3.6, 2.8, 2.5 respectively; $P < 0.01$). The lowest rates (1.54) were observed in Jewish women born in Yemen [17]. It seems, therefore, that there are not only marked differences in incidence between Jewish and non-Jewish women, but also considerable differences between various Jewish ethnic groups. The reason for these inter-ethnic differences has not yet been clarified.

Many attempts have been made to identify the cause of the remarkable infrequency of carcinoma of the cervix among Jewish women. This quest is of great general importance, since an explanation for this phenomenon might contribute to a better understanding of the process of carcinogenesis and possibly assist in the prevention of the neoplasm. The low occurrence of cervical cancer in Jewish women has been variously attributed to traditional habits, to different risk factors, or to genetic factors that provide some degree of resistance or immunity.

Traditional habits

Jews around the world practice two distinct traditional habits: the ritual circumcision of males 8 days after birth, and the prohibition by the family purity laws (*Niddah*) against sexual intercourse both during menses and 7 days after its complete cessation.

Circumcision

The low incidence of cervical cancer in Jewish women has been ascribed to maximal circumcision of Jewish male infants [18]. However, others subsequently concluded that non-circumcision does not increase the risk of cervical cancer [19]. It is beyond the scope of the present survey to review the innumerable studies dealing with the association between circumcision and cervical cancer. Many of the studies were performed in non-Jewish women, or compared non-circumcised Christian populations with circumcised Moslem populations, or non-circumcised Hindu populations with Moslem populations. The findings of these epidemiologic studies are often conflicting. The reason for the inconsistent results is that attempts to assess the association between the circumcision status of the male partner and cervical cancer encountered several difficulties [20]. Many confounding factors were not accounted for, and when multiple partners were involved the issue became even more complicated. Many women did not know the circumcision status of their sexual partner. In addition, there may have been discrepancies between men's reports of their circumcision status and the results of examinations. Finally, the degree of circumcision was not uniform. It has therefore been suggested that circumcision studies should be based on actual examination of the male partners. Such a study was conducted by Terris et al. [20], who found no significant differences in the circumcision status of the first marital partners of women with invasive and pre-invasive cervical lesions and controls matched by age and ethnic group. The circumcision status of the partners of the few Jewish women included in the study was not specified. Another example of a study negating the association was performed in Lebanon [21]. This population-based study found that notwithstanding the circumcision status of men, cervical carcinoma was as frequent in Moslems as in Christians. There was also no difference between cases and controls in circumcision status of the husband as determined by physical examination. The data by Stewart et al. [12] also yielded no support for a relationship between lack of circumcision and cancer of the cervix in non-Jewish white women. They found that among Jewish women in Israel, only 1 of the 48 with cancer of the cervix stated that she had had intercourse with an uncircumcised male. Of the Jewish women in New York City, 7 of 46 cases (15.2%) and 1.7% of controls gave a history of intercourse with one or more uncircumcised partners. This difference was significant ($P < 0.01$). However, the higher rate of intercourse with uncircumcised males in the cases may be a reflection of the liberal sexual habits in this group and not of the circumcision status of their partners. It should also be mentioned that the incidence of cervical cancer among Israeli Jewish female immigrants from the former Soviet Union, some of whom are married to uncircumcised men, is not different to that in the general population [22].

Although the dispute over the association of circumcision and cervical cancer in various populations is still ongoing [23,24], there seems to be no hard evidence that circumcision prevents its occurrence in Jewish women, and it is no longer considered to play a protective role.

Abstinence from intercourse

Among orthodox Jewish women who observe the laws of *Niddah*, cervical cancer is even less common than in the rest of Israeli Jewish women. This observation seems to support the notion that abstinence from intercourse during and for several days after menses is a protective factor. However, it is extremely difficult to isolate this ritual from other risk factors that are absent in the orthodox group, such as early coitarche, multiple partners, and smoking. A similar low occurrence has been found in other communities with strict sexual conduct that practice endogamy – i.e., marrying within their faith [25], but do not practice circumcision. The data by Stewart and co-workers [12] also failed to show any significant association between cancer of the cervix and abstinence from intercourse during or after menses in Israeli Jewish women and Jewish women in New York City, as well as in non-Jewish white women. It should also be mentioned that the great majority of Israeli Jewish women no longer practice the laws of *Niddah*, yet the incidence of cervical cancer among them remains persistently low.

Risk factors

General risk factors

No difference between Jewish and non-Jewish women has been found with regard to general risk factors for cervical carcinoma. Comprehensive epidemiologic studies by Martin in the U.S. [25] and by Pridan and Lilienfeld in Israel [26] indicated that like other populations, cervical cancer in Jewish women is associated with younger age at first coitus and first marriage, a higher number of sexual partners, and lower socioeconomic status.

Herpes simplex virus type 2 infection

For almost a decade the sexually transmitted HSV-2 was implicated in the etiology of cervical carcinoma and has been the subject of detailed investigations [27,28]. The association between HSV-2 and cervical cancer was also assessed in Israeli Jewish women. Menczer et al. [29] examined HSV-2 titers in sera from 39 Jewish women with cervical cancer, in sera from controls hospitalized for benign gynecologic diseases, matched by age and country of origin, and in sera from the general population of healthy female subjects. The HSV-2 titers were significantly higher in patients than in controls, and in the range of reported rates in cervical carcinoma patients in other populations. On the other hand, the HSV-2 titers in the general female population were low compared to many other demographic areas. The authors suggested that the low incidence of cervical cancer among Jewish women may be related to the low reservoir of the HSV-2 virus in the general population. These findings contradicted another study in Israeli Jewish women in which the percentage of HSV-2-positive controls resembled that in the cervical cancer cases [26].

It is now generally accepted that HSV-2 plays no major role in the etiology of cervical cancer, except perhaps as a co-factor in a limited number of patients [30], or as an initiating agent [31]. The low reservoir of HSV-2 therefore does not explain the infrequency of cervical cancer in Jewish women.

Human papillomavirus infection

Currently, it is widely accepted that degradation of the *p53* suppressor gene by oncogenic HPV E6 early protein plays a crucial role in the etiology of cervical cancer [3–5]. Oncogenic HPV was found in about 90% of cervical carcinoma tissue samples in many demographic areas [31]. Previously, using the Southern blot hybridization technique, a low (36%) prevalence rate among 22 Israeli cervical carcinoma patients had been reported [32]. However, another recent study, using a sensitive polymerase chain reaction technique, found that, as in other populations, the prevalence of HPV in cervical cancer cases is very high [33]. In the general Israeli population the prevalence of HPV, as assessed by filter *in situ* hybridization of cervical smears, was found to be low [34]. Whether this affects the frequency of cervical cancer in Israeli Jewish women is not clear.

Genetic factors

Hochman et al. [7] contend that the equal incidence of cervical cancer in the Ashkenazi and non-Ashkenazi ethnic groups is clear evidence that the low cervical cancer incidence in Jewish women is not a genetic or racial phenomenon. On the other hand, Stewart et al. [12] proposed that the similar incidence rate in the various groups of Jewish women studied in New York and Israel support the assumption that the disease is infrequent because of a genetically determined lack of susceptibility.

p53 polymorphism

In 1998, Storey and associates [35] reported that the presence of homozygous arginine polymorphism at codon 72 of *p53* represents a significant risk factor in the development of HPV-associated cervical carcinoma. If this observation is valid, then a low prevalence of this polymorphism in Jewish women might constitute the genetic basis for the low incidence among them. Thus, it was of tremendous interest to assess the prevalence of the homozygous arginine polymorphism in healthy Israel Jewish women, and the association between the presence of this polymorphism and cervical cancer in Jewish women. We recently performed such an investigation [36]. Our study group included 23 Israeli Jewish patients with histologically confirmed squamous cell carcinoma of the cervix. The control group comprised 162 randomly chosen Israeli Jewish healthy women, considered to represent the general population. The germline *p53* polymorphism at codon 72 was determined by PCR in DNA obtained from a blood sample taken from each subject. In this study, Arbel-Alon et al. [36] showed that among healthy Israeli Jewish women, the prevalence of the arginine homozygous *p53* polymorphism paralleled the pattern of cervical carcinoma in the Israeli population. While lower than in other populations, it was significantly higher in women of North Africa origin than in the other ethnic groups (30.3 vs. 10.8%, $P < 0.01$). Furthermore, the association between the homozygous arginine polymorphism and cervical cancer, as reported by Sorey et al. [35], was also found in Israeli Jewish women.

These findings support the possibility that the low prevalence of the homozygous arginine polymorphism may play a role in determining the low incidence of cervical cancer in Jewish women and may also explain the differences between the ethnic groups. If these observations are confirmed, then the low incidence of cervical cancer in Jewish women is genetically determined, and an explanation for the ethnic incidence pattern of cervical cancer in Jewish women has also finally been found.

Conclusions

For many years it was predicted, on the basis of observations in selected cohorts or individual institutions, that the incidence of invasive cervical carcinoma in Israeli Jewish women will increase [37–39]. While ritual circumcision is still practiced widely, today only a minority of Jewish women observes the laws of *Niddah*. Sexual habits have also changed considerably, becoming far less stringent. In spite of these trends of the last four to five decades, the population-based incidence of cervical cancer in Israeli Jewish women has not increased and remains very low [22,40].

HSV-2 = herpes simplex virus type 2
HPV = human papillomavirus

PCR = polymerase chain reaction

Braithwaite [6], who first noted the low incidence in Jewish women in 1901, suggested two explanations for this "immunity." The first was the difference of race, and the second the difference in diet, namely the "absence of bacon and ham in the diet of Jews." He then added: "The latter is far more probable than the former, although there may be something in race." Now, a century after Braithwaite's original observation, it seems that there may indeed be something in "race."

References

1. Rigoni-Stern D. In: Rotkin Ricci JV, ed. One Hundred Years of Gynaecology, 1800-1900. Philadelphia: Blackstone Co. 1945.
2. Gagnon F. Contribution to the study of the etiology and prevention of cancer of the cervix of the uterus. *Am J Obstet Gynecol* 1950;50:516–22.
3. Bosch FX, Manos M, Munoz N, et al. Prevalence of human papillomavirus in cervical cancer: a worldwide perspective. *J Natl Cancer Inst* 1995;87:796–802.
4. Pfister H. The role of human papillomavirus in anogenital cancer. *Obstet Gynecol Clin North Am* 1996;23:579–95.
5. Bosch FX, Munoz N, de Sanjose S. Human papillomavirus and other risk factors for cervical cancer. *Biomed Pharmacol* 1997;51:268–75.
6. Braithwaite J. Excess of salt in the diet: a probable factor in the causation of cancer. *Lancet* 1901;ii:1578–80.
7. Hochman A, Ratzkowski E, Schreiber H. Incidence of carcinoma of the cervix in Israel. *Br J Cancer* 1955;9:358–64.
8. Kennaway EL. Racial and social incidence of cancer of the uterus. *Br J Cancer* 1948;2:177–22.
9. Wynder EL, Cornfield J, Schroff PO, Doralswami KP. A study of environmental factors in carcinoma of the cervix. *Am J Obstet Gynecol* 1957;68:1016–24.
10. Terris M, Oalman MC. Carcinoma of the cervix; an epidemiologic study. *JAMA* 1960;175:155–61.
11. Brzezinski A, Bromberg YM. Significance of postmenopausal genital bleeding in Jewish women. *Obstet Gynecol* 1953;1:359–63.
12. Stewart HL, Dunham J, Casper J, et al. Epidemiology of cancers of the uterine cervix and corpus, breast and ovary in Israel and New York City. *J Natl Cancer Inst* 1966;37:1–8.
13. Steinitz R, Costin C. Cancer in Israel, facts and figures 1960-1966. Jerusalem: Ministry of Health, and Israel Cancer Association, 1971.
14. Modan B, Sharon Z, Shani M, Sheba Ch. A comparison of some epidemiological aspects of cervical and endometrial carcinoma. *Path Microbiol* 1970;35:192–7.
15. Sharon Z, Shani M, Modan B. Clinicoepidemiologic study of uterine cancer. Comparative aspects of the endometrial and cervical sites. *Obstet Gynecol* 1977;50:536–40.
16. Menczer J, Modan B, Oelsner G, Sharon Z, Steinitz R, Sampson S. Adenocarcinoma of the uterine cervix in Jewish women. A distinct epidemiologic entity. *Cancer* 1978;41:2464–8.
17. Steinitz R. Five year morbidity from neoplasms in Israel's population groups (1960-1964). Jerusalem: Ministry of Health, 1967.
18. Dunn JE, Buell P. Association of cervical cancer with circumcision of sexual partner. *J Natl Cancer Inst* 1959;22:746–9.
19. Rotkin ID. A comparison review of key epidemiologic studies in cervical cancer related to current searches for transmissible agents. *Cancer Res* 1973;33:1353–67.
20. Terris M, Wilson F, Nelson J. Relation of circumcision to cancer of the cervix. *Am J Obstet Gynecol* 1973;117:1056–66.
21. Abou-Daoud KT. Epidemiology of carcinoma of the cervix uteri in Lebanese Christians and Moslems. *Cancer* 1967;20:1706–14.
22. Barchana M, Andreev H, Alon R. Israel Cancer registry. Cancer in Israel 1994. Jerusalem: Ministry of Health, 1997.
23. Brinton LA, Reeves WC, Brenes MM, et al. The male factor in the etiology of cervical cancer among sexually monogamous women. *Int J Cancer* 1989;44:199–203.
24. Agarwal SS, Sehgal A, Sardana S, Kumar A, Luthra UK. Role of male behavior in cervical carcinogenesis among women with one lifetime partner. *Cancer* 1993;72:1666–9.
25. Martin CE. Marital and coital factors in cervical cancer. *Am J Public Health* 1967;57:803–14.
26. Pridan H, Lilienfeld M. Carcinoma of the cervix in Jewish women in Israel, 1960-1967. An epidemiological study. *Isr J Med Sci* 1971;7:1465–70.
27. Rawls WE, Tompkins WA, Figueroa ME, Melnick JL. Herpesvirus type 2: association with carcinoma of the cervix. *Science* 1968;161:1255–6.
28. Royston I, Aurelian L. The association of genital herpesvirus with cervical atypia and carcinoma in situ. *Am J Epidemiol* 1970;91:531–8.
29. Menczer J, Leventhon-Kriss S, Modan M, Oelsner G, Gerichter CB. Antibodies to herpes simplex virus in Jewish women with cervical cancer and in healthy Jewish women of Israel. *J Natl Cancer Inst* 1975;55:3–6.
30. Zur Hausen H. Human genital cancer: synergism between two virus infections or synergism between a virus infection and initiative agents? *Lancet* 1982;ii:1370–3.
31. Galloway DA, McDougal JK. The oncogenic potential of herpes simplex virus: evidence for a "hit and run" mechanism. *Nature* 1983;302:21–4.
32. Mitrani-Rosenbaum M, Gal D, Friedman M, et al. Papillomaviruses in lesions of the lower genital tract in Israeli patients. *Eur J Cancer Clin Oncol* 1988;24:725–35.
33. Menczer J, Fintsi Y, Arbel-Alon S, et al. The presence of HPV 16,18 and immunohistochemical staining in tumor tissue of Israeli Jewish women with cervical and vulvar neoplasia. *Eur J Gynecol Oncol* 2000;21:30–4.
34. Isacsohn M, Dolberg L, Gottschalk Sabag S, et al. The inter-relationship of herpes virus, papilloma 16/18 virus infection and Pap smear pathology in Israeli women. *Isr J Med Sci* 1994;30:383–7.
35. Storey A, Thomas M, Kalita A, et al. Role of a p53 polymorphism in the development of human papilloma virus-associated cancer. *Nature* 1998;393:229–34.
36. Arbel-Alon S, Menczer J, Feldman N, Glezerman M, Yeremin L, Friedman E. Codon 72 polymorphism of p53 in Israeli Jewish cervical cancer patients and healthy women. *Int J Gynecol Cancer* 2002; 12:741–4.
37. Schachter A, Avraham A. Changing trends of cervical neoplasms in Israeli Jews. *Lancet* 1984;ii:1150.
38. Baram A, Schachter A. Cervical carcinoma: disease of the future for Jewish women. *Lancet* 1982;I:747–8.
39. Glezerman M, Piura B, Insler V. Cervical cancer in Jewish women. *Am J Obstet Gynecol* 1989;161:1186–90.
40. Menczer J, Modan M, Katz L. Cervical cancer in Israel. *Lancet* 1983;i: 875.

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Brevity is the soul of lingerie

Dorothy Parker (1893-1967), American humorist and champion of liberal causes. She died a depressed alcoholic.