CHAPTER 14

Genital Cancers, Females: Relation with Medical Radiation, and Discussion

• Part 1. How a Dose-Response Fails to Develop, 1921-1940

Female genital cancers include cancers of the cervix uteri, corpus uteri, ovaries, fallopian tubes, broad ligament, and other female genital organs (see Chapter 4, Part 5, Number 9).

Inspection, of the 1940 MortRates in Table 14-A, shows that the 1940 Hi5/Lo4 MortRate ratio is near unity (1.04). We have not seen such a low ratio in any of the previous chapters. Because the response (cancer MortRate) is so nearly alike in the Nine Census Divisions, it is highly unlikely that any significant dose-response exists in these data. And indeed, regression analysis confirms the absence of any dose-response. (We do not show the standard ten regressions in this chapter. Of course, the y-values are always the 1940 MortRates from Table 14-A, and the x-values are always the ten familiar sets of PhysPops, from Table 3-A.)

The summary-results of the regression analyses are presented in Box 1. In the maximum relationship (2j), the two measures of significance are both exceedingly low. The highest R-squared value is 0.0683. The highest ratio of the X-Coefficient over its Standard Error is 0.7163.

Box 2 prepares the input for Figure 14-A. As expected, Figure 14-A shows nine boxy symbols which predict a line of best fit which is nearly flat. In other words, an increment in dose (PhysPop) hardly produces any increment in response (MortRate).

Before moving to other considerations, we further explored the absence of a dose-response for female Genital Cancers by regressing the non-white 1940 MortRates upon PhysPop. Like the all-race MortRates for 1940, the non-white MortRates come from Grove 1968, Table 67. Although the Hi5/Lo4 ratio for the non-white study-group is 1.35 instead of 1.04, the correlation of the non-white 1940 MortRates with PhysPop is just as poor as it is for the all-race MortRates:

Census Div.	1940 PhysPop	1940 MortRate
Pacific	159.72	33.9
New England	161.55	60.4
WestNoCentral	123.14	65.0
Mid-Atlantic	169.76	55.8
EastNoCentral	133.36	61.3
Mountain	119.89	27.5
WestSoCentral	103.94	45.6
EastSoCentral	85.83	46.0
So Atlantic	100.74	44.9

Genital Ca, non-white Females: Regression Output:	
Constant	36.7668
Std Err of Y Est	13.3506
R Squared	0.0484
No. of Observations	9
Degrees of Freedom	7
X Coefficient(s)	0.0946
Std Err of Coef.	0.1586
XCoef/S.E. =	0.5964

Among all the cancers studied in this monograph, female Genital Cancers turn out to be the ONLY group of cancers whose 1940 MortRates have no significant relationship with PhysPop (Chapter 22, Box 1). What are the possible explanations?

"Small numbers" are clearly not the explanation for the absence of any significant dose-response. The 1940 female MortRates for Genital Cancers are many times higher than the female MortRates for Urinary Cancer in Chapter 12 --- where a strong dose-response develops by 1940. We see no reason to think that the absent dose-response reflects misdiagnosis of female Genital Cancers. And there is no reason to believe that the female pelvis escaped exposure to medical irradiation, inasmuch as it received exposure from xrays of the hip, lumbar spine, lumbo-sacral spine, kidney-ureter-bladder, lower gastro-intestinal tract, pelvimetry, etc. We note that significant dose-responses occur for both digestive-system and urinary-system cancers in females (Chapters 10 and 12).

For female genital cancers, the absence of a dose-response is not a marginal matter. The results do not fall BARELY below some arbitrary level of statistical significance. The difference from every other set of cancers is like "night versus day."

• Part 2. The Subsets of Female Genital Cancers

We wish to ascertain which was the most important subset of female Genital Cancers in 1940. Grove 1968 (in Table 65, p.589), provides National 1940 MortRates for three groups of female Genital Cancers per 100,000 population (male + female), which is why the total rate of 16.0 (shown below) is approximately HALF of the National values in our Table 14-B. In 1960, Grove's Table 65 (p.597) provides separate entries for four groups of female Genital Cancers, so we will examine the 1960 entries, too. Although the 1960 entries are not age-adjusted to the 1940 reference year, we can use them "as is" to calculate percentages:

100.0%	16.0	= 1940 MortRate for all female Genital Cancers.
79.4%	12.7	= 1940 MortRate for cancer of the uterus (corpus + cervix).
17.5%	2.8	= 1940 MortRate for cancer of ovary, fallopian tube, and parametrium.
3.1%	0.5	= 1940 MortRate for cancer of vagina, vulva, and unspecified sites.
100.0%	13.0	= 1960 MortRate for all female Genital Cancers.
36.2%	4.7	= 1960 MortRate, malignant neoplasm of cervix uteri.
25.4%	3.3	= 1960 MortRate, malignant neoplasm of other parts of the uterus.
34.6%	4.5	= 1960 MortRate, malig. neoplasm of ovary, fallopian tube, broad ligament.
3.8%	0.5	= 1960 MortRate, malig. neoplasm of unspecifed female genital organs.

In both 1940 and 1960, the two major parts of the uterus (cervix and corpus) dominate the cancer death-rates in the grouping called female Genital Cancers. And in the uterus, the cervix accounts for more cancer mortality in 1960 than does the corpus. It is noteworthy that, by 1988, age-adjusted MortRates from Ovarian Cancer and from Uterine Cancer (including Cervical Cancer) had become approximately equal (our Figure 67-A). During the 1940-1988 period, MortRates from Ovarian Cancers increased somewhat, while MortRates from Uterine Cancers fell drastically. A contribution to the latter's fall may have come from a high rate of womb-removal in the USA.

• Part 3. Findings in the Most Recent Report on A-Bomb Survivors

Naturally, we wondered what the findings are for induction of female Genital Cancers by bomb-radiation in the A-Bomb Survivor Study.

The most recent follow-up (1950-1990) of the A-Bomb Survivors is presented in Pierce 1996-b. There (at page 15), we find Table X, "Numbers of Cancer Deaths and One-Sided P-Values for a Dose-Effect." The P-value for cancer of the uterus (cervix + corpus) is presented as 0.092. The P-value for cancer of the ovary is presented as 0.010. With one result (uterus) statistically suggestive and the other (ovary) statistically significant, the message is VERY different from the findings in our Box 1 --- where statistical significance is not even approached at all.

This difference is a clue of some sort. One would expect the statistically stronger results to occur in the larger study, all other things being equal. But we find the reverse, even though our xray study has millions of female participants and the A-Bomb Study has only about 50,000 females --- most of whom were hardly irradiated at all by the bomb (Chapter 2, Part 5a).

In view of the results in the A-Bomb Study, as well as the 1940 results in our studies for all cancers EXCEPT female Genital Cancers, we would expect to find a significant and positive dose-response relationship between medical radiation (PhysPop) and female Genital Cancers. Therefore, one ought to ask: What might make it appear that this relationship does NOT exist, if it DOES exist?

If the nine dose-groups (the populations of the Nine Census Divisions) happen to be badly matched for nonxray causes of female Genital Cancers, the bad matching could explain the complete absence of a dose-response in our Box 1 of this chapter. The effect of poor matching can vary in degree, of course. In Chapter 5, our Figure 5-D illustrates degradation of statistical strength from perfection (R-squared = 1.00) to a strength which is still highly significant (R-squared = 0.7112). Our Figure 5-E illustrates that an INVERSE relationship, between PhysPop and some other powerful cause of the same cancers, can even make a truly positive dose-response between medical radiation and those cancers appear to be negative. Between these extreme illustrations lies a range of concealment where poor matching just makes a signficant positive dose-response appear to be non-existent (so that the line of best-fit is approximately flat, with about the same response at all dose-levels).

Parts 4 and 5 discuss, for illustrative purposes, two of the several nonxray causes of female Genital Cancers which might be badly matched across our nine dose-groups. We emphasize "might," because we doubt very much that any useful data exist on the geographical distribution of these two causes before (or after) 1940.

• Part 4. Ovarian Cancer and Talcum Powder

For decades, there has been suspicion that the substance, talc, might be gaining access to the ovary by the vagina-uterus-oviduct route, and that talc might be an ovarian carcinogen.

4a. The Background as Presented by Cramer et al, 1982

Daniel W. Cramer and associates begin their 1982 paper by stating (Cramer 1982, p.372): "The possibility that ovarian cancer may be caused by exposure to certain hydrous magnesium silicates such as talc and asbestos has been raised by several researchers (Graham 1967 + Henderson 1971 + Longo 1979). The lack of epidemiologic studies regarding this hypothesis prompted us to investigate talc exposures in a case-control study of ovarian cancer." In their discussion, they state (Cramer 1982, p.375):

"The argument linking talc and ovarian cancer includes four elements: The chemical relationship between talc and asbestos, asbestos as a cause of pleural and peritoneal mesotheliomas, the possible relationship between epithelial ovarian cancers and mesotheliomas, and the ability of talc to enter the pelvic cavity. The mineral talc is a specific hydrous magnesium silicate chemically related to several asbestos group minerals and occurring in nature with them. Generic 'talc' is seldom pure and may be contaminated with asbestos, particularly in powders formulated prior to 1976 (Cralley 1968 + Rohl 1976)." And they add (Cramer 1982, p.375):

"Although greeted with skepticism, the finding of talc particles embedded in normal and abnormal ovaries suggests that talc is a substance that can enter the pelvic cavity via the vagina (Henderson 1971)."

4b. Results of the Talc Study by Cramer et al. 1982

The Cramer study compared 215 white females with epithelial ovarian cancers with 215 control women from the general population matched by age (average age = 53), race, residence, educational level, and religion. They were not matched for parity, however (Table 1). Relative risks had to be adjusted for this and some other "potential confounders" (Cramer 1982, p.373). Results:

"Ninety-two of the cases (42.8%) regularly used talc either as a dusting powder on the perineum or on sanitary napkins compared with 61 (28.4%) controls. Adjusted for parity and menopausal status, this difference yielded a relative risk of 1.92 ($P < 0.003$) for ovarian cancer associated with these practices. Women who had regularly engaged in both practices had an adjusted

relative risk of 3.28 ($P < 0.001$) compared to women with neither exposure. This provides some support for an association between talc and ovarian cancer ... The authors also investigated opportunities for potential talc exposure from rubber products such as condoms or diaphragms or from pelvic surgery. No significant differences were noted between cases and controls in these exposures ..." (Cramer 1982, p.372). In the end, they conclude (Cramer 1982, p.376):

"If talc is involved in the etiology of ovarian cancer, it is not clear whether this derives from the asbestos content of talc or from the uniqueness of the ovary which might make it susceptible to carcinogenesis from both talc and other particulates." And (p.376): "It is hoped that this report will stimulate further study of talc exposure in relation to ovarian cancer."

Exposure to genital powders is very common among American women (Part 4c, below).

4c. Results of the Powder and Spray Study by Cook et al. 1997

Linda S. Cook and colleagues begin their 1997 paper as follows (Cook 1997, p.459):

"Studies documenting the migration of carbon particles and radioactive particulate agents from the vagina to the ovaries (2 references), as well as those that have identified talc-like particles more frequently in ovarian tumors than in normal human ovarian tissue (1 reference), have raised concern that genital powder exposure may increase a woman's risk of developing ovarian cancer. While the results of several epidemiological studies have suggested elevated risks for ovarian cancer among women with genital powder exposures (8 references), results have been inconsistent for particular methods of powder application (1 reference). In this population-based case-control study, information on the method, duration, and frequency of powder application was collected to evaluate the impact of genital powder exposures on the risk of epithelial ovarian cancer." Their study consisted of 313 ovarian cancer cases and 422 controls. One of the featured results (Cook 1997, p.459):

"After adjustment for age and other methods of genital powder application (none vs. any), an elevated relative risk of ovarian cancer was noted only for women with a history of perineal dusting (RR = 1.6, 95% CI 1.1-2.3) or use of genital deodorant spray (RR = 1.9, 95% CI 1.1-3.1). These results offer support for the hypothesis, raised by prior epidemiologic studies, that powder exposure from perineal dusting contributes to the development of ovarian cancer, and they suggest that use of genital deodorant sprays may do so as well."

At the end of their paper, Cook and co-workers urge additional studies, and point out (Cook 1997, p.465):

"The prevalence of genital powder exposure reported among control women in this and other studies conducted in the United States ranges from 28 percent to 51 percent (5 references). Given such a common practice, even the modest elevation of ovarian cancer risk associated with genital powder application suggested by most of the epidemiologic studies could have a notable impact on the incidence of ovarian cancer in the United States."

• Part 5. Cervical Cancer and Human Papilloma Virus ... and Co-Actors

There seems to be little doubt that infection of the female genital tract, with human papilloma viruses (HPV), plays a very important role in the causation of squamous-cell carcinoma of the cervix ("cervical cancer"). Dr. Keerti Shah comments on some of the recent findings in an editorial in the New England Journal of Medicine (Nov. 6, 1997). Indeed, Shah states (Shah 1997, p.1387): "In all parts of the world, infections with genital HPVs appear to account for nearly 100 percent of cervical cancers (Bosch 1995 and unpublished data)." And (p.1387): "In most cancers, the HPV genome is integrated into the cellular DNA."

Among about 30 strains of HPV which can infect the cervix, only a few strains --- most especially HPV-16, 18, 31, and 45 --- seem to be carcinogenic. A 1998 study indicates that infection even by these "high-risk" HPV strains often clears up (Ho 1998, p.424, Table 1.)

Several lines of evidence indicate that the HPV virus needs help from carcinogenic co-actors, in order to produce a case of fatal cervical cancer (ZurHausen 1998). For example, work by Apple (1994, 1995) suggests that a woman's particular mixture, of inherited genes for HLA proteins, has an

influence on her risk of developing cervical cancer after cervical infection with HPV-16. Other recent work (Storey 1998) suggests that women who inherit a particular variant of the p53 gene are most at risk for the CONSEQUENCES of infection by the "high-risk" HPV strains.

Prokopczyk, another investigator into the etiology of cervical cancer, explicitly asserts that HPV infection by itself is not enough to cause cervical cancer in women. He suggests: "There must be another factor initially damaging the cervical DNA" (Prokopczyk 1996, p.282). Some experimental work with mice (Arbeit 1996) also seems to suggest that HPV alone does not suffice. According to Prokopczyk and colleagues (Prokopczyk 1997, p.869):

"HPV-modified DNA has been detected in up to 93% of cervical tumor specimens (IARC 1995 + Bosch 1995). However, because HPV infections are widespread in the general population and HPV-immortalized cell lines are generally not tumorigenic, HPV infection likely interacts with one or more co-factors before cancer develops." They mention deficiency in micronutrients, lower socioeconomic status, use of oral contraceptives, and cigarette smoking as co-factors which have been explored.

With respect to smoking, they state (Prokopcyzk 1997, p.869): "Winkelstein (1990) reviewed 18 studies of cigarette smoking and cervical cancer: 15 of these studies supported an increased risk (up to 4.3-fold higher) of cervical cancer among smokers, and several of these studies demonstrated a dose-response relationship (2 references). Environmental exposure to cigarette smoke has also been suggested to increase the risk of cervical cancer (Slattery 1989) ..." Later (at p.872), Prokopcyzk et al report that "Smoking-related DNA damage has been demonstrated by several studies (5 references) through P-32 postlabeling techniques; however, structures of these putative adducts remain unknown."

These workers undertook a small pilot study in which they found that that cervical mucus, from women who smoke, contains a significantly higher concentration of a carcinogenic tobacco-specific nitrosamine (NNK) than cervical mucus from nonsmokers (Prokopcyzk 1997, p.871, Table 1).

- Part 6. A Likely Explanation for the Absent Dose-Response

Cancer is a disease having multiple causes. Indeed, co-action among two or more causes may be required to produce most of the fatal cases. In every chapter of Section 2 except this chapter, we find that medical radiation was a NECESSARY cause in a very high fraction of all cancers which were fatal in 1940.

We doubt very much that medical radiation plays no role at all in female Genital Cancers. We think the probable explanation, for the absence of any dose-response in these data, is bad matching (across the Nine Census Divisions) of some co-actors which are potent in causing female Genital Cancers but are not potent in causing the other cancers. There is no doubt that badly matched dose-groups can mask a true dose-response beyond detection. This is such a common pitfall, in human epidemiological research, that it is reasonable to suspect it to be the explanation here.

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Box 1 of Chap. 14

Summary: Regression Outputs, Genital Cancers, Females.

Below are the summary-results from regressing the 1940 cancer MortRates upon the ten sets of PhysPops (1921-1940).

Part	PhysPop	R-squared	Constant	X-Coef	Std Err	X-Coef/SE
2a	1921	0.0006	31.06	0.0034	0.0529	0.0643
2b	1923	0.0020	30.77	0.0058	0.0493	0.1171
2c	1925	0.0163	29.56	0.0155	0.0454	0.3410
2d	1927	0.0262	29.18	0.0188	0.0433	0.4340
2e	1929	0.0318	29.05	0.0200	0.0417	0.4798
2f	1931	0.0427	28.89	0.0211	0.0378	0.5587
2g	1934	0.0534	28.92	0.0208	0.0331	0.6285
2h	1936	0.0458	29.19	0.0185	0.0320	0.5793
2i	1938	0.0539	29.13	0.0189	0.0299	0.6316
2j --->	1940 Max	0.0683	29.06	0.0191	0.0267	0.7163

Box 2 of Chap. 14

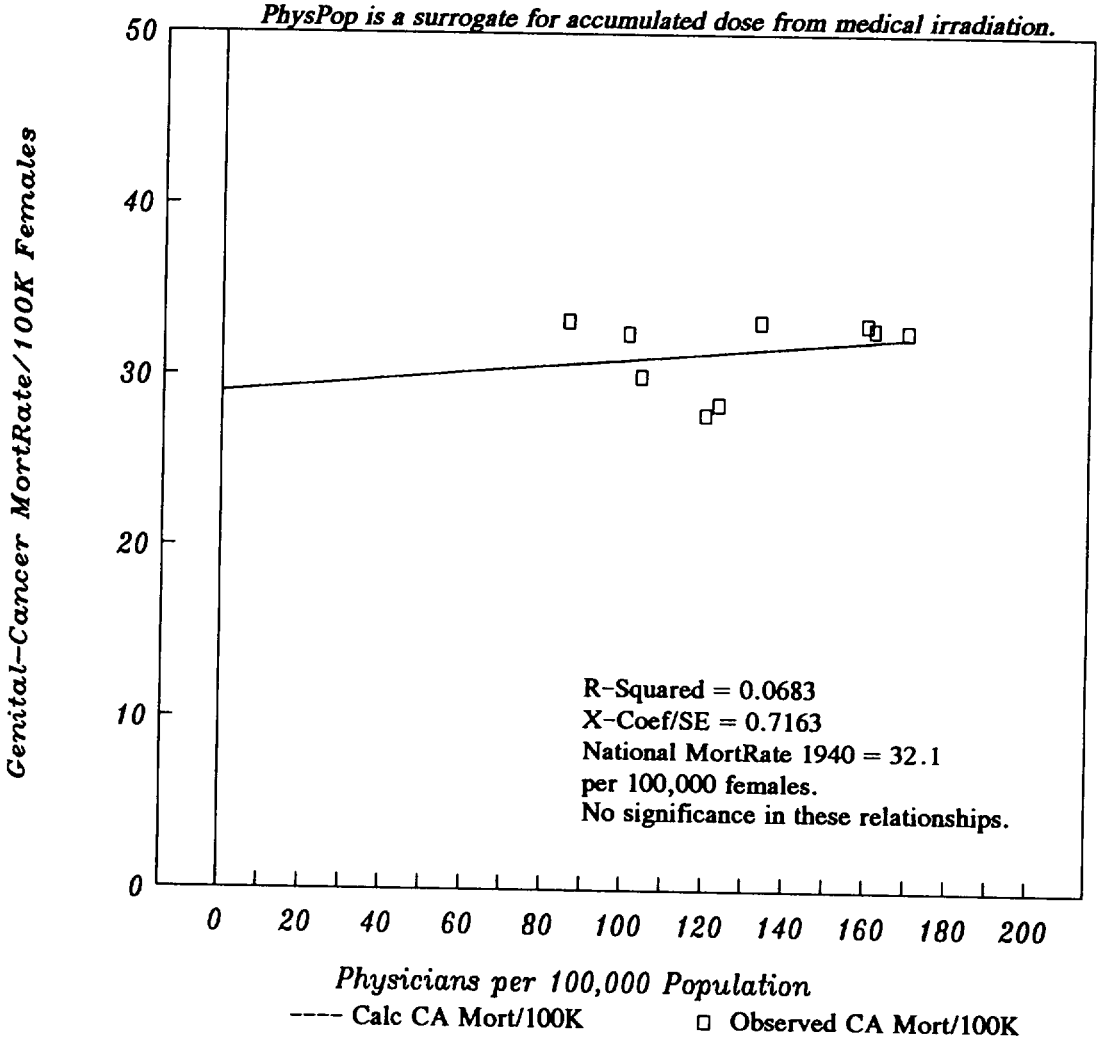
Input-Data for Figure 14-A. Genital Cancers. Females.

Part 2j, Best-Fit Equation: Calc. MortRate = (0.0191 * 1940 PhysPop) + (29.06)

Census Divisions	1940 Observed PhysPops	1940 Observed MortRates	Best-Fit Calc. MortRates
Pacific	159.72	33.1	32.111
New England	161.55	32.8	32.146
West No. Central	123.14	28.4	31.412
Mid-Atlantic	169.76	32.7	32.302
East No. Central	133.36	33.2	31.607
Mountain	119.89	27.8	31.350
West So. Central	103.94	30.0	31.045
East So. Central	85.83	33.2	30.699
South Atlantic	100.74	32.5	30.984
Additional PhysPops	70.00		30.397
--- not "observed" ---	60.00		30.206
down to zero PhysPop	50.00		30.015
(zero medical radiation).	40.00		29.824
For each, we calculate	30.00		29.633
a best-fit MortRate.	20.00		29.442
These additional x,y pairs	10.00		29.251
are also part of the	0		29.060
best-fit line (Chap 5, Part 5e).			

1940 Genital-System Cancer Mortality-Rates versus 1940 PhysPop Values for the 9 Census Divisions, USA.

Dose-Response Relationship



On the X-axis, PhysPop values = Physicians per 100,000 Population in the Nine Census Divisions of the USA Population, Year 1940. This variable is a surrogate for accumulated radiation dose --- the more physicians per 100,000 people, the more radiation procedures are done per 100,000 people.

On the Y-axis, Genital-Cancer Mortality-Rate per 100,000 females = the reported rates in USA Vital Statistics for the Nine Census Divisions, Year 1940, for all "races" combined, no exclusions.

Shown above is the strongest relationship between these two variables (Part 2j). The nine datapoints (boxy symbols) were collected long ago for other purposes, and are free from potential bias with respect to this dose-response study. There is no dose-response relationship detected with these data, so the presumptive Fractional Causation in 1940 by medical radiation is zero.

Table 14-A.

Genital Cancer Mortality Rates by Census Divisions: Females.

Rates are annual deaths per 100,000 female population, USA, age-adjusted to the 1940 reference year. Sources are provided in Chapter 4, Part 2. There are no exclusions by color or "race." The tabulation includes averages (not population-weighted) and the Hi5/Lo4 ratios --- explained at the outset of Chapter 4.

Census Division	1940	1950	1960	1970	1980	1990
Pacific	33.1	25.5	20.0	16.7	13.3	--
New England	32.8	25.1	21.7	17.6	13.4	--
West North Central	28.4	23.4	20.3	16.8	13.3	--
Mid-Atlantic	32.7	27.2	22.2	18.3	14.3	--
East North Central	33.2	28.3	24.2	19.4	14.5	--
Mountain	27.8	23.6	18.4	15.0	11.7	--
West South Central	30.0	27.4	22.1	17.3	12.5	--
East South Central	33.2	29.7	24.7	19.5	14.3	--
South Atlantic	32.5	29.9	24.0	18.8	13.5	--
Average, ALL	31.5	26.7	22.0	17.7	13.4	--
Average, High-5	32.0	25.9	21.7	17.7	13.8	--
Average, Low-4	30.9	27.7	22.3	17.7	13.0	--
Ratio, Hi5/Lo4	1.04	0.94	0.97	1.00	1.06	--

Table 14-B.

Genital Cancer Mortality Rates, USA National.

Rates are age-adjusted to the 1940 reference year. Both sexes: Deaths per 100,000 population (males + females). Males: Deaths per 100,000 male population. Females: Deaths per 100,000 female population. No exclusions by color or "race."

	Both Sexes	Male	Female
1940	23.5	15.2	32.1
1950	21.0	14.9	27.2
1960	18.5	14.6	22.4
1970	--	14.8	18.0
1979-81	13.5	15.0	13.7
1990	--	16.9	--

- 1940, 1950, 1960: All rates come from Grove 1968, Table 67, p.693, "Malignant neoplasms of genital organs (171-179)" ICD/7.
- 1970: All rates are interpolations (Chap. 4, Parts 2b, 2c).
- 1980: All rates (ICD/9, 179-187) come from the reference NatCtrHS 1980.
- 1990 male rates by Divisions and National come from Monthly Vital Statistics Vol.43, No.8, January 31, 1995. Females: Not available.