

Primary Peritoneal Serous Carcinoma in Men: A Rare and Non-*BRCA*-associated Entity

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Abstract. *Background:* Primary peritoneal serous carcinoma (PPSC) is a rare neoplasm. The paucity of reported cases among men may provide insight to the cell of origin of PPSC. *Materials and Methods:* A search for the ICD 0-3 code of PPSC (C48.2) in the following datasets: the Israeli National Cancer registry (INCR), the Surveillance, Epidemiology, and End Results (SEER) database in the USA, Israeli male *BRCA* carriers, male high-risk and *BRCA* carriers in a USA study, and the Italian Study on Male Breast Cancer (MBC) were performed. *Results:* In the INCR dataset, 220 entries for C48.2 code were noted, with only one male (male:female ratio=0.0045). In the SEER dataset for histology codes of papillary/serous/ adenocarcinoma, 2,673 cases were recorded, with five males (male:female ratio=0.0018). None of the recorded US or Italian male *BRCA* carriers or MBC, or Israeli male *BRCA* carriers was diagnosed with PPSC. *Conclusion:* PPSC is a rare neoplasm, seemingly not associated with *BRCA* mutations in men, and fallopian tube epithelial cell implants may contribute to its development.

Primary peritoneal serous carcinoma (PPSC), or papillary serous carcinoma of the peritoneum, is a rare, intra-abdominal neoplasm, with an age-adjusted incidence rate in the US is 6.78 per million (1). PPSC diagnosis carries a

grave prognosis, with a 5-year survival of less than 20% in affected women (2). PPSC has been presumed to arise from extraovarian mesothelium that has a Mullerian potential or endometriosis involving the peritoneal surface (3-5). Yet because of its rarity, little is known about the molecular mechanisms that underlie the development of PPSC.

PPSC is overwhelmingly diagnosed in women, with a propensity in female *BRCA1* or *BRCA2* gene mutation carriers, even after risk-reducing bilateral salpingo-oophorectomy (RRBSO). Casey and co-workers reported a 3.5% risk over 20 years for developing PPSC in *BRCA* mutation carriers after RRBSO, with more cases noted in *BRCA1* carriers compared to *BRCA2* carriers (6). Rebbeck *et al.* reported a rate of 0.8% in *BRCA* carriers diagnosed up to 8.6 years after RRBSO (7). Among unselected, average-risk women who underwent salpingo-oophorectomy for non-cancer reasons, the rate of PPSC is minimal: 1/4128 cases with a median follow-up of 7.2 years after BSO that was carried out not in the context of risk reduction (8). The paucity of reported cases among men (9-11) raises interesting issues: Should PPSC be included in the spectrum of cancers that affect men as well as women? What is the rate of this rare tumor in male *BRCA* carriers and males from high-risk, non-*BRCA* families? What is the gender ratio of this diagnosis on a national cancer registry level? The current study was undertaken to shed light on these issues in order to provide more insight into the pathogenesis of these tumors.

Materials and Methods

In order to maximize the ability to analyze the rate of PPSC in males, we queried several datasets: the INCR and the Surveillance, Epidemiology, and End Results (SEER) datasets (datasets that include all consecutive cancer diagnoses in Israel and the USA, respectively), the dataset at the Oncogenetics unit at the Sheba

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Key Words: Primary peritoneal serous carcinoma, PPSC, ovarian cancer, male *BRCA* mutations, cancer risk.

Medical center of male *BRCA* carriers, the dataset of a USA based study on male breast cancer cases, and the Italian National Study of Male Breast Cancer.

Israel. The study was approved by the Sheba Ethics Committee (SMC 1493-2000). A cross referencing of all individuals registered in the context of the Israeli National Cancer registry (INCR) since its establishment in 1960 with the International Classification of Disease (ICD 0-3) code C48.2, was carried out and the sex of the individuals was obtained. No other details were available from this source. The INCR, a passive, national, population-based cancer registry, was established in 1960. Since 1982, reporting on all cancer cases to the INCR is compulsory by law. The INCR completeness with respect to patients with solid tumors is over 96.8% (12).

BRCA carriers. A cross-referencing of all male carriers of *BRCA1* or *BRCA2* mutation genotyped and identified at the Oncogenetics Unit, at the Sheba Medical Center since 1996 with the INCR was performed, as previously described (13), using the specific ICD 0-3 codes and the histological subtypes relevant to PPSC: 8260/3: papillary adenocarcinoma, non-otherwise specified (NOS); 8441/3: serous cystadenocarcinoma, NOS; 8460/3: papillary serous cystadenocarcinoma.

The SEER program database. The SEER database (www.seer.cancer.gov-Research Data released April 2016, based on the November 2015 submission) was queried for ICD 0-3 code 48.2. Subsequent analysis was restricted to histological codes 8260/3: papillary adenocarcinoma, NOS; 8441/3: serous cystadenocarcinoma, NOS; 8460/3: papillary serous cystadenocarcinoma.

Italy. Male breast cancer (MBC) cases (either population- or clinic-based series) were recruited from Italian Investigation Centers in different areas of the country in the framework of the collaborative Italian Multicenter Study on MBC (14). For each MBC case, information on personal and family history of cancer and *BRCA* mutational status was collected by a geneticist and validated by the relevant sources, mainly local Cancer and Mortality Registries. *BRCA1* and *BRCA2* mutation analysis was performed in the context of genetic counselling programs at the local medical centers for all MBC cases and unaffected relatives. The Italian Multicenter study on MBC was approved by the local Ethical Committee (Sapienza University of Rome, Protocol 264/12). Written informed consent was obtained from all study participants.

United States. MBC cases: MBC cases were recruited from State Cancer Registries in Utah and the surrounding intermountain states (Colorado, Idaho and Wyoming), an on-line male support group and referrals from physicians and family members. The participants were enrolled under Institutional Review Board approval (IRB 09180) and all signed informed consent. Cases referred by family members were from breast cancer families and the remaining cases were unselected for age or family history of breast cancer as previously described (15). Cancer status was through the individual, relatives, or the Utah Cancer Registry for those residing in Utah.

Male members of BRCA1 and BRCA2 families: Male individuals of families carrying pathogenic mutations in *BRCA1* and *BRCA2* were identified. From linkage in the Utah Population Database, within these families, information on cancer status was extracted. Cancer status for the participants was through the individual, relatives, or the Utah Cancer Registry.

Results

Israel. The INCR encompasses ~800000 entries since 1960, ~45% of which refer to men. There were 220 cases of code C48.2 in the entire cohort: 219 in women and one in a man (male:female ratio=0.0045). In all likelihood, this was the same case described by Shmueli *et al.* in 2001 (11). None of the 237 *BRCA1/BRCA2* carriers genotyped at the Oncogenetics Unit developed cancer bearing the same code during a mean of 9.2 years of follow up.

SEER database. The total number of malignancies registered in SEER was 8,234,845 (4,227,600 in males). Search of individuals diagnosed with code 48.2 yielded 7,087 cases, including 6,041 females and 1,046 males. Search restricted to histology codes given above resulted in 2,673 cases, including 2,668 females and five males (male:female ratio=0.0018) For men, age at diagnosis ranged from 57 to 73 years.

Italy. A total of 624 men affected with breast cancer, including nine *BRCA1* and 79 *BRCA2* mutation carriers were recruited. Age at first breast cancer diagnosis ranged between 22 and 91 years, with a mean age of 61.6 years. An additional 219 male *BRCA* mutation carriers who were family relatives of male breast cancer cases, including 107 with *BRCA1* and 112 with *BRCA2* mutation were recruited. Age at recruitment ranged between 20 and 86 years, with a mean age of 47 years. At the time of *BRCA* genotyping or diagnosis of breast cancer, none was diagnosed with PPSC. No follow-up data were available for these individuals.

United States. One hundred and fifteen male breast cancer cases were recruited from the above-mentioned sources (see Materials and Methods above): the 10 cases referred by family members were from breast cancer families and the remaining 105 cases were unselected for age or family history of breast cancer. Within the 105 male breast proband families, there were 1966 males. From 203 families carrying pathogenic mutations in *BRCA1* and *BRCA2*, there were a total of 7817 males for whom we had information on cancer status.

Of a total of 9783 males in our *BRCA1* and *BRCA2* families or families ascertained for a male-breast proband, there were no recorded or reported cases of PPSC at the time of last contact or cancer registry linkage in 2002. No follow-up data were available for these individuals.

Discussion

This study supports the common notion that PPSC is indeed a rare disease, with the overwhelming majority of diagnosed cases being women. It is also apparent that being a male *BRCA1* or a *BRCA2* mutation carrier or even being clinically defined as having high cancer risk with no known *BRCA*

mutation in men is not associated with any clinically significant risk for developing this rare entity.

Peritoneal epithelial cells originate from the embryonic mesonephric structures (16) in both men and women. Certain male reproductive organs differentiate from the mesonephric system, including the epididymis, vas deferens, and seminal vesicles. Yet PPSC is extremely rare in males.

The differences in the rates between men and women could be accounted for by several factors including: hormonal exposure, genetic factors and the presence of Mullerian-derived intraperitoneal cell implants that may be gender specific. Indeed, Dubeau (17) suggested that the cell of origin in ovarian carcinoma and PPSC is derived from the primary and secondary Mullerian system (paramesonephric) and not from the epithelial cells lining the ovaries and peritoneum. One plausible explanation to account for the vastly divergent rates in males and females of PPSC diagnosis is that this tumor indeed arises from cells implanted on the peritoneum that may originate, at least in part, from cells that were shed from the fallopian tubes in women, or from the secondary Mullerian system (microscopic structures lined by Mullerian epithelium). Male sertoli cells, secrete Mullerian-inhibiting substances (MIS) starting at the seventh week of gestation, inducing Mullerian system regression. Levels peak early in postnatal life, decline during puberty due to the inhibitory effect of testosterone, and remain relatively stable through adulthood and always higher than the levels in women (18). MIS may contribute to the lack of growth of Müllerian system-derived tumors in males. Indeed, monoclonal antibody anti-Müllerian-inhibiting substance type II receptor (MISRII) showed promise in treating ovarian granulosa cells and epithelial cell tumors in mice (19). Vaccination with anti MISRII significantly inhibited tumor growth when administered either prophylactically or therapeutically to mice (20). Such a notion of the pathogenesis of PPSC is consistent with the diagnosis of PPSC within a few years following RRBSO.

Another plausible explanation to account for PPSC diagnosis in men is persistent remnant Mullerian duct syndrome (PMDS MIM # 261550). This is a rare genetic condition leading to the presence of Müllerian duct derivatives in phenotypical males. It is hypothesized that PMDS is the result of MIS deficiency, receptor mutation, or pure lack of expression of MIS *in utero* (21). Yet all these hypotheses should be viewed as speculative since there are no data presented herein to substantiate these notions. Furthermore, at least some PPSCs that have been analyzed histopathologically seem to have distinct molecular features compared with epithelial and intra-fallopian tumors (22).

The limitations of this study should be noted. For *BRCA* carriers from the USA and Italy, there were no follow-up data, so the lifetime risk for developing PPSC in these high-risk individuals is still unknown. The risk for developing ovarian cancer depends, in part, on the location of the

specific mutation, which may be different in the various *BRCA* mutation carriers from ethnically-diverse populations compared with the rather limited spectrum of mutations in Jewish Ashkenazi individuals. An additional limitation is that there was no independent pathology review of all the reported cases. Thus, in the reported Israeli male case, p53 immunohistochemistry, the most common pathological feature of PPSC (22) was not rechecked (11).

In conclusion, PPSC is a rare neoplasm, seemingly not associated with *BRCA* mutations in men, and in women, the cell of origin may be of Müllerian tube origin, possibly with some contribution of fallopian tube-originated epithelial cell implants, especially in *BRCA* mutation carriers.

Conflicts of Interest

All Authors declare that they have no conflicts of interest in regard to this study.

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