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| **ANSWER KEY for “Breast Cancer Risk: Using Real Medical Histories to Rank Genetic and Environmental Influences”**  by **Michèle Shuster**, Department of Biology, New Mexico State University, Las Cruces, NM **Karen Peterson**, Human Biology Division, Fred Hutchinson Cancer Research Center, Seattle, WA |

**Preparatory Reading Assignment**

1. How do age at menarche and age at menopause affect breast cancer risk?

Starting to menstruate early (before 12 years of age) and having a late menopause (later than age 55) both increase breast cancer risk (because these increase the total lifetime exposure to estrogen).

2. What are the genes that are most commonly mutated in hereditary breast cancer? Approximately what percent of all breast cancers are hereditary?

BRCA1 and BRCA2 are the most commonly mutated genes in hereditary breast cancer. Hereditary breast cancer accounts for between 5 and 10% of all breast cancers.

3. How does a woman’s weight influence her breast cancer risk?

Being obese after menopause increases breast cancer risk because adipose tissue is a source of estrogen—the more adipose tissue there is, the more estrogen that continues to be produced after menopause. (Note that before menopause, estrogen is produced by the ovaries; menopause is when the ovaries stop making estrogen.) Being obese prior to menopause actually decreases risk by causing irregular periods.

4. If you were a physician taking a family history to assess breast cancer risk in a patient, what information would you want to know and why would you want to know it?

I would want to know the patient’s racial or ethnic background, as the risk of developing or dying from breast cancer differs in different populations.

I would want to know if any first-degree relatives (mothers, sisters) had breast cancer, and if so, how many first degree relatives, and the age at which their cancer developed. The more relatives affected (especially first degree relatives) and the earlier that a breast cancer develops, the higher the risk to other family members (because of a suspected strong family genetic pre-disposition).

I would then ask about other relatives who have had breast cancer (males and females), and about ovarian cancer in the family. These also increase the risk.

5. How do pregnancy and HRT influence breast cancer risk?

* Earlier and multiple pregnancies decrease breast cancer risk.
* Waiting until after about age 30 to have a first child does not reduce breast cancer risk (in fact, it slightly increases risk).
* Never having children increases breast cancer risk.
* HRT (hormone replacement therapy), in particular combination therapy (estrogen and progesterone), increases the risk of developing breast cancer and of dying from breast cancer. The breast cancers that develop in women using combination HRT seem to be more aggressive and harder to detect at an early stage, leading to a poor prognosis.

**Risk Assessments**

**Ana’s Profile**

Based on the National Cancer Institute’s “Cancer risk: Understanding the puzzle” (<http://understandingrisk.cancer.gov/a_Breast/00.cfm>; accessed 5/30/2007).

Ana is a 64 year old woman in generally good health.

Being over the age of 60 puts her at increased risk of developing breast cancer.

She had her first child when she was 20.

This actually reduces her risk.

She entered menopause at the age of 58.

This increases her risk, as she entered menopause after the age of 55.

She has been on hormone replacement therapy since entering menopause (for the past 6 years).

This increases her risk (especially as she has been taking them for more than 5 years).

She has gained some weight since menopause.

This increases her risk, due to increased estrogen production from adipose tissue.

Her mother had breast cancer at the age of 37.

This increases her risk, as it is a first-degree relative diagnosed under the age of 40.

**Risk Assessments**

**Paula’s Profile**

Based on Ryan et al. 2006. Case 6-2006: A 71-year-old woman with urinary incontinence and a mass in the bladder. *New England Journal of Medecine* 354:8.

Paula is 71 years of age, and currently has a urinary bladder tumor, with metastases in the ovaries and possible involvement of one lymph node.

Her age puts her at increased risk for breast cancer (but see her personal history below).

Paula had breast cancer 22 years ago (at age 49). She was treated with chemotherapy and bilateral (both breasts) mastectomy. At the time of her initial diagnosis, four positive lymph nodes were found.

She has a personal history of breast cancer, which increases her risk, and the positive lymph nodes suggest invasive (if not necessarily metastatic) cancer.

Paula’s sister was diagnosed with breast cancer three years ago, then ovarian cancer two and a half years ago.

She also has a first-degree relative with breast and ovarian cancer, which also increases her risk (although we don’t know the age her sister was at the time of her breast cancer diagnosis).

Paula’s mother died of lung cancer.

Two maternal uncles had pancreatic cancer.

Her maternal aunt had myeloma.

Her maternal grandmother had uterine cancer.

The above four points indicate cancer in her family, but different types (not breast or ovarian). So this may not speak directly to breast cancer risk.

Paula’s sister had genetic testing, and was found to have a BRCA1 mutation.

BRCA1 mutations can play a role in breast cancer, so her sister’s breast cancer may have an inherited basis (inheritance of a mutant BRCA1 allele).

Paula’s sister has one daughter (Paula’s niece).

This does not influence Paula’s current breast cancer risk, but this daughter should be considered in the follow-up recommendations.

After her sister’s genetic testing, Paula had genetic testing, and the same BRCA1 mutation as her sister was detected in Paula.

If the sister’s BRCA1 mutation was causative in her breast cancer, then Paula appears to have inherited the same allele. This could contribute to Paula’s overall risk.

Paula has one daughter.

As we don’t know the age of the daughter (and therefore Paula’s age when she had her), the daughter herself doesn’t contribute to Paula’s breast cancer risk. However, like her cousin (Paula’s niece), Paula’s daughter should be considered in the follow-up recommendations.

**Advanced Discussion Points for Paula**

Paula’s “bladder” cancer was in fact determined to be metastatic breast cancer (from her original breast cancer). Testing of the tumor showed it to be estrogen receptor-positive (ER-positive), and Paula was started on treatment with tamoxifen. In a more advanced class, the assays to detect ER-positive tumors could be discussed, as could the mechanism of action of tamoxifen (and why it would not be effective on ER-negative tumors). More advanced students could explore the clinical trials literature on tamoxifen (see the additional references provided in the Teaching Notes).

Although both Paula and her sister had the same BRCA1 mutation, it was a missense mutation (not a nonsense mutation). The mutation has been observed in other cancer patients, but in combination with additional BRCA1 mutations. The implications of missense as compared to nonsense mutations could be discussed, as could the clinical relevance of mutations, and how such relevance can be established (see the additional references provided in the Teaching Notes).

**Nora’s Profile**

Based on Ryan et al. 2003. Case 28-2003: A 51-year-old premenopausal woman with newly diagnosed breast cancer and a strong family history of breast cancer. *New England Journal of Medecine* 349:11.

Nora is a 51 year-old, pre-menopausal woman.

Her age is not yet a strong risk factor for breast cancer (compared to a woman over the age of 65), and if she enters menopause in the next 3 to 4 years, she will not be at increased risk in that regard (so she is not past the point of “late menopause”).

She had her first period at the age of 13.

This is not early enough to increase her risk.

She has had two pregnancies (and has one child), the first pregnancy was when she was 32.

While we don’t know if the first or second pregnancy resulted in a child being born, the fact that she was 32 for the first pregnancy does slightly elevate her breast cancer risk (if this was the pregnancy that resulted in a child), as it was after the age of 30. If the second pregnancy resulted in the child, and if that pregnancy occurred after the age of 35, then this would be an even higher elevation of risk.

She used oral contraceptives for six years.

As long as it has been 10 years since she stopped taking the oral contraceptives, this is not a risk factor for breast cancer.

She has not taken any hormone-replacement therapy (HRT).

This is a risk-reduction for her (assuming she does not initiate HRT upon reaching menopause).

She smoked until age 26.

This is not a risk factor for breast cancer. (However it does not reduce the risk either!)

She consumes between 1 and 4 alcoholic drinks per week.

This is not a sufficient alcohol intake to increase her risk.

Her mother had breast cancer at 48 years of age, and now has lymphoma (at age 72).

This is a first-degree maternal relative with breast cancer, thus her risk is increased.

Her maternal grandmother had breast cancer at age 47, and now has lung cancer.

This is another relative (also on the maternal side) with breast cancer.

Her paternal first cousin presently has breast cancer (at the age of 30).

This is another relative (on the paternal side) with breast cancer at a very young age.

Her paternal aunt died “at a young age” from breast cancer.

This is another relative (on the paternal side) with early breast cancer. The number of more distant relatives with young-onset breast cancer certainly increases her risk.

Her father was of Ashkenazi Jewish heritage, and died of colon cancer at 66 years of age.

While her father did not die of breast cancer, his background, in combination with the strong family history of female breast cancer on his side of the family, suggests that there may be a genetic component, at least on his side of the family (e.g. BRCA1 or BRCA2).

**Advanced Discussion Points for Nora**

Nora had, in fact, been recently diagnosed with breast cancer and was being treated for her cancer at the time of the published report. In her case, all her strong risk factors did result in breast cancer at the age of 51. In a majors introductory biology course, or a genetics course, students could be asked to draw a pedigree for this family (based on cancer history). Note that a pedigree is presented in the Ryan et al. (2003) article (see figure 2, page 1078). This pedigree could be used as an answer key for this activity.

Based on her family history, and the Ashkenazi Jewish ancestry of her father, Nora elected to undergo genetic testing for BRCA1 and BRCA2. The paper discusses looking for founder mutations first (given her father’s heritage), as well as the important role of genetic counseling in genetic testing. This could provide discussion points for the concept of founder mutations, the functional significance of mutations, the risks and benefits of genetic testing as well as the idea of looking for specific mutations rather than sequencing an entire gene.

Nora was found to have a specific BRCA2 mutation that occurs in approximately 1% of people of Ashkenazi Jewish descent. Based on her personal history and the results of the genetic testing, Nora elected to have a bilateral (both breasts) mastectomy as a prophylactic measure. Students could contemplate what they would do in this situation, they could discuss the implications for other family members (now that there is a known mutation in the family), and the implications of a BRCA2 mutation on ovarian cancer risk (it turns out that she also decided to have an oophorectomy). In this case, the prophylactic mastectomy appears to have been a good decision, as additional carcinomas in situ and additional areas of hyperplasia were found in the excised tissue from *both* breasts.

**June’s Profile**

Based on Ryan et al. 2005. Case 24-2005: A 58-year-old woman with early-stage estrogen-receptor-positive breast cancer. *New England Journal of Medecine* 353:6.

June is 58 years old.

Her age is not yet a strong risk factor for breast cancer (compared to a woman over the age of 65).

She has been having “regular” mammograms (at two to three year intervals), and the one from two and a half years ago did not show an abnormal mass.

While she has been having mammograms, she has not been having them yearly.

Her first period was at age 13.

This is not early enough to elevate her risk.

She has had two pregnancies, resulting in two children, the first of which was at age 27.

This is not late enough to be considered a risk-elevating factor.

She experienced menopause at age 51. She did not take hormone replacement therapy (HRT), but she used oral contraceptives for a total of four years in the past.

Her menopause was not “late” in terms of cancer risk. The fact that she has not taken HRT reduces her risk, and as long as she has not taken oral contraceptives for an extended period of time, they do not substantially elevate her risk.

She has high blood pressure and high cholesterol.

While these do not necessarily bode well for her general health, they do not specifically adversely affect her risk for breast cancer.

She has low levels of thyroid hormones.

This is not a specific risk factor for breast cancer.

She also has “weak bones.”

While this may be indicative of osteoporosis, it is not a specific risk factor for breast cancer.

Her maternal aunt died of breast cancer in her 30’s.

This is a second-degree relative with early-onset breast cancer, which represents a slight elevation of breast cancer risk.

Her mother died of a brain tumor at age 39.

A first degree relative died of cancer (but not breast or another reproductive cancer). This is slightly harder to assess, but likely is not as strong a risk factor as having a first degree relative with breast cancer.

Her father is alive and well at age 84.

This does not adversely affect her breast cancer risk. (Her father seems to be quite healthy!)

**Rankings of Relative Breast Cancer Risk**

While these are subjective, and while these cases were not in actuality compared “head to head,” one possible ranking with respect to breast cancer risk is as follows (with the relative ranking of Nora and Paula open for consideration):

Nora

She has a very strong family history of breast cancer. Her first pregnancy was a little on the late side.

Paula

Strong personal history of breast cancer. Family cancer history, but not all breast cancer.

Ana

Overall quite healthy, with her major risk factor being her mother’s (a first degree relative) breast cancer (diagnosed under the age of 40).

June

Her strongest risk factor is a second-degree relative who died of breast cancer in her 30s.

**Possible Recommendations**

Nora

Based on her family history, she should continue to have regular (annual) mammograms.

Based on her family history and heritage, she may want to consider BRCA1/BRCA2 gene testing (in a setting with genetic counseling).

If those results are positive, she may want to consider other options (including e.g. prophylactic mastectomy).

Paula

Her personal history is positive for breast cancer, although that was nearly 50 years ago.

She should have her current tumor be the highest priority for her medical care, and be sure that her medical history is available to her physicians.

Given that Paula’s sister is BRCA1 positive, her sister’s daughter (Paula’s niece) should be made aware of a possible increase in breast cancer risk.

Given Paula’s BRCA1 status, her daughter may want to consider BRCA1 testing, as well as vigilant mammography.

Ana

She may want to consider stopping her HRT.

She could probably benefit from losing some weight.

Given her personal and family medical history, she should be encouraged to get regular mammograms.

June

She is quite healthy, and has one second-degree relative with breast cancer.

She should probably increase her frequency of mammograms (to once a year).

She should probably work on her general health (exercise and diet) to enhance her overall health.